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THE BLOOD VOLUME IN CHRONIC ARTHRITIS.

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A disturbance of the blood supply to the affected joints is apparent in many cases of chronic arthritis. Pemberton[1] has thoroughly studied this physiologic phase of the disease and has stressed its importance. Pemberton and others[2] have reproduced in the dog the bone changes characteristic of hypertrophic arthritis in man by ligating the vessels which carry the blood supply to the patella. In atrophic arthritis there is much clinical evidence of a diminished blood flow to the joints; the extremities are typically cold and cyanotic, and direct signs of a disturbed circulation may be obtained by studying the surface temperature and observing the superficial capillaries by means of the microscope. Fundamental improvement in the condition of a patient suffering from atrophic arthritis can usually be gauged by the state of the circulation around the joints.

Several explanations have been suggested for the diminished blood supply in the joints. Hypertrophic arthritis is often observed in association with arteriosclerosis and hypertension. In such cases the actual vascular disease may be the cause of a decrease in the flow of blood to the joints, which interferes with the nutrition of the cartilage. A marked anemia would also be an evident factor

in the nutrition of joint tissues. Increased tone of the sympathetic innervation and consequent vasoconstriction of the arterioles supplying the joints may account for a decreased blood flow as is shown by the beneficial results of ganglionectomy in properly selected cases of atrophic arthritis. It is also conceivable that an actual variation in the total volume of blood may account, in part at least, for the diminished vascularity.

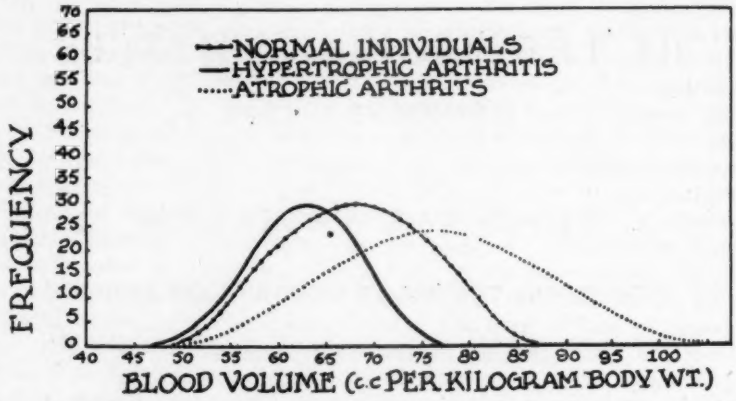

FIG. 1.—Smoothed curves of frequency distribution of blood volume determinations in normal individuals and in different types of arthritis.

To obtain further data on this last possibility, blood volume determinations have been made in 41 unselected cases of chronic arthritis of the two types.

The colorimetric method of Rowntree, Brown and Roth,[3] using Congo red (National anilin, Schultz No. 307), was employed. A 1.5 per cent solution of the dye in distilled water was made each day and sterilized by bringing it to the boiling point twice. The exact amount of solution delivered from the 18-cc. graduation mark on a 20-cc. record syringe was determined and each patient was given this amount intravenously. This is an accurate and simple method for determining the exact amount of dye introduced into the blood stream. Exactly 4 minutes after the injection blood was withdrawn from the other arm without the use of a tourniquet. Rowntree employs a 2-minute interval. Other workers,[4,5] have found that mixing is not complete under 4 minutes. The patient was kept in bed for at least ½ hour before the test.

Normal Findings. Determinations of the blood volume were made in the case of 16 normal individuals (Table 1). The average whole blood volume was found to be 67 cc. per kg. Rowntree, Brown and Roth[3] found 88.6 cc. of whole blood per kg. as the average normal for men, and 85.7 cc. for women. Another worker[6] with the dye method reports a volume of from 81.8 to 93 cc. as normal. The results obtained by the carbon monoxid method are

much lower, however, varying from 59.4[7] to 71.4[7] per kg. Our figures for the normal by the dye method are lower than the findings of others. This might be due in part to the fact that we employ a 4-minute interval instead of a 2-minute interval. The same technique was used throughout, however, so that the comparative value of the estimations is unimpaired. We have repeated determinations on the same individuals at intervals of several months and have obtained close checks. (Table 2.)

TABLE 1.—BLOOD VOLUMES IN NORMALS.

Sex.	Blood volume, cc.	Per kg., cc.	Per sq. m., cc.	Plasma volume, cc.	Per kg., cc.
M	3936.1	67.0	2139.0	2361.7	37.5
M	4729.6	55.0	2413.6	2606.0	30.3
M	5331.5	71.1	2820.9	2345.9	31.2
M	5761.5	56.5	2216.0	2707.9	26.5
F	4107.0	72.7	2566.9	2464.2	42.5
M	4950.3	72.3	2705.1	2747.4	40.1
F	3649.6	64.0	2294.7	2080.3	36.5
M	5788.4	62.9	2643.1	3241.5	35.2
M	4227.5	68.9	...	2409.7	39.3
M	5351.7	73.8	2846.6	2782.9	38.4
F	3915.0	66.9	2509.6	2505.6	42.8
M	4517.4	57.2	2455.1	2303.9	29.2
F	3752.5	78.1	2501.3	2251.5	46.8
F	3672.4	71.3	2400.2	2247.5	43.6
F	3768.3	75.3	2479.1	2185.6	43.7
M	5047.7	64.7	2549.3	2832.8	36.3
Average	4531.6	67.0	2502.7	2504.6	37.5

TABLE 2.—SUCCESSIVE BLOOD VOLUMES IN THE SAME NORMAL INDIVIDUALS.

	Total plasma vol., cc.	Plasma, vol. per kg., cc.	Total blood, vol., cc.	Blood, vol. per kg., cc.	Blood, vol. per sq. m., cc.
Dr. R. L. S.:					
Dec. 29, 1931	2409.6	39.3	4227.5	68.9	2562.1
Mar. 13, 1931	2312.8	37.7	3920.0	63.9	2375.7
Miss R. W.:					
Feb. 6, 1931	2505.6	42.8	3915.0	66.9	2509.6
Apr. 22, 1931	2455.7	43.1	3837.0	67.3	2491.5

Findings in Arthritis. The results of determinations made in the case of 26 patients suffering from atrophic arthritis are shown in Table 3. The average blood volume is 75.9 cc. per kg. The highest volume is 112 cc. and the lowest 57 cc. per kg. This is a wide variation but in 20 cases the blood volume was between 65 and 85 cc. per kg. The average blood volume in this group of cases was found to be greater than that in the normal group; it is apparent, therefore, that a decrease in blood volume plays no part in the diminished blood flow to the affected joints.

In the group of 15 patients suffering from hypertrophic arthritis the average blood volume was found to be slightly less than that in the normal group. As shown in Table 4, the average blood volume in the hypertrophic group is 62.5 cc. per kg., with a variation of from 49.8 to 76.3 cc. There is no great variation in the average

for the series. Overweight individuals have a smaller blood volume per kilogram than normal persons. This fact probably explains our findings in this group, since patients with hypertrophic arthritis tend to be above the average weight. Only a relatively small percentage of our group of patients with atrophic arthritis were underweight, therefore a variation in weight cannot be the explanation for the increased blood volume observed in the atrophic cases.

TABLE 3.—BLOOD VOLUMES IN ATROPHIC ARTHRITIS.

Case No.	Sex.	Blood volume, cc.	Per kg., cc.	Per sq. m., cc.	Plasma volume, cc.	Per kg., cc.
2	M	4593.3	60.8	2367.7	2756.0	36.5
4	M	5582.4	66.5	2877.5	2819.1	33.6
5	M	4625.8	75.2	2705.1	2863.4	46.5
6	M	5512.6	72.5	2826.9	3015.1	39.6
7	F	3947.5	78.1	2580.1	2759.3	54.6
8	M	5042.6	72.0	2725.7	2743.2	39.2
9	F	4264.7	58.2	2352.9	2686.8	36.5
10	M	5058.4	84.3	3201.5	3490.3	58.1
14	M	4894.4	75.3	2749.6	3377.0	52.0
15	M	5065.6	73.4	2680.2	2781.0	40.3
16	F	4907.9	81.8	2956.6	3224.5	53.7
23	M	5071.8	76.2	2857.3	3093.8	46.5
26	F	3577.6	71.5	2353.7	2310.4	46.2
28	F	4670.0	57.0	2419.7	3042.2	37.1
32	M	4467.2	84.3	2713.4	2680.3	50.6
35	F	4156.4	100.1	2927.0	2909.5	70.1
38	F	3881.0	84.4	2752.4	2600.3	56.5
40	F	4667.9	68.1	2667.4	2940.8	42.9
43	M	5228.8	84.3	3022.4	3226.2	52.0
45	M	6147.8	88.4	3152.7	3713.3	53.4
46	F	3848.4	74.0	2515.3	2511.9	48.3
47	M	6252.8	112.6	3932.5	4189.4	75.5
48	F	4034,0	76.8	2689.3	2299.4	43.0
50	F	5051.3	74.3	2988.9	3384.4	49.8
51	F	3759.5	66.5	2364.5	2392.1	42.8
52	F	6050.1	57.6	2880.0	3751.1	35.7
Average		4793.1	75.9	2779.2	2983.1	47.7

TABLE 4.—BLOOD VOLUMES IN HYPERTROPHIC ARTHRITIS.

Case No.	Sex.	Blood volume, cc.	Per kg., cc.	Per sq. m., cc.	Plasma volume, cc.	Per kg., cc.
1	M	4131.8	49.8	2174.6	2148.6	25.8
3	F	3555.2	55.1	2061.7	2062.0	31.9
11	F	3500.9	66.6	2318.5	2205.6	42.0
12	M	3933.4	79.4	2675.8	2198.8	44.4
13	F	3999.7	59.2	2311.9	2439.8	36.2
18	F	4829.2	60.4	2624.5	2559.5	31.9
19	F	3527.8	52.6	2120.9	2116.7	31.6
27	F	2928.9	57.4	1952.6	1815.9	35.6
30	F	3170.8	59.1	2086.1	1870.8	35.0
31	M	3506.2	68.0	2177.8	1858.3	34.1
33	M	5344.0	63.6	2726.5	3206.4	38.2
44	F	4123.4	76.3	2767.3	2515.3	46.5
49	F	4302.2	58.9	2376.9	2710.4	37.1
37	F	3910.1	61.5	2313.7	2424.3	38.2
41	M	4646.9	65.9	2640.3	2277.0	32.3
Average		3960.7	62.5	2355.3	2293.9	36.1

The increased blood volume in the cases of atrophic arthritis is due entirely to an increase in the plasma portion. The average plasma volume is 47.7 cc. per kg., as contrasted with 37.5 cc. in normal individuals. In hypertrophic arthritis the plasma volume is 36.1 cc. per kg. The comparative figures on the total plasma and cell volumes are summarized in Table 5. In atrophic arthritis an oligocythemic hypervolemia is present and in hypertrophic arthritis there is an oligocythemic hypovolemia.

TABLE 5.—SUMMARY.

	Total blood volume, cc.	Total plasma volume, cc.	Total cell volume, cc.
Normals	4531.6	2504.6	2027.0
Atrophic arthritis	4783.1	2983.1	1800.0
Hypertrophic arthritis	3960.7	2293.9	1666.8

Since the total blood volume in atrophic arthritis is greater than that in normal individuals, with a decrease in blood in the peripheral vessels, the excess blood must be held in the large splanchnic vessels. This factor may account for the beneficial effects of breathing and postural exercises which aid in the mobilization of these large, relatively stagnant, visceral pools.

Summary. Blood volume determinations made by the Congo red method in 26 patients suffering from atrophic arthritis and 15 with hypertrophic arthritis are reported. The average blood volume in the atrophic group was found to be 11.8 per cent above the average for normal individuals, and in the hypertrophic cases 6.7 per cent below the normal average.

The increase in blood volume in atrophic arthritis is due to an increase in plasma volume, and cannot be explained on the basis of decreased body weight.

The decreased vascularity of the affected joints in atrophic arthritis cannot be due to a decrease in total blood volume.

The evident diminished blood supply to the peripheral vessels with an increased blood volume in atrophic arthritis is probably best explained by the stagnation of blood in the splanchnic pool.

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STREPTOCOCCIC AGGLUTINATION IN CHRONIC ARTHRITIS AND ACUTE RHEUMATIC FEVER.

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The value of streptococcic agglutination in differentiating the various classes of nonspecific chronic arthritis from one another and from arthritis in any way associated with rheumatic fever has recently received important consideration as the result of the work of Dawson, Olmstead and Boots,[1] and Nicholls and Stainsby.[2] The results of the latter suggested different etiologic agents for proliferative arthritis, degenerative arthritis, polyarthritis following rheumatic fever, and arthritis immediately associated with acute rheumatic fever. Streptococcic agglutinins have been found in the serums in a few cases of acute rheumatic fever[3] but, on account of the small number studied, no definite conclusions were reached concerning the significance of the presence of these agglutinins.

The agglutination reaction as a means of classifying streptococci has been studied by different workers in the past. The literature on this subject, which will not be discussed in this paper, has recently been reviewed in the Annals of the Pickett-Thomson Laboratory.[4] It can be said, however, that the agglutination reaction has not proved a sufficient means of grouping streptococci with any degree of uniformity into classes which bear a definite relation to habitat, pathogenesis, or etiology of lesions.

Streptococci have been recovered from the blood, joints, lymph nodes, and subcutaneous nodules in a relatively high percentage of the cases of chronic arthritis, and from the blood, joints, and subcutaneous nodules in acute rheumatic fever. The frequent finding of streptococci in the above sources suggested an etiologic relationship. We attempted, therefore, to see if we could collect further evidence by the agglutination reaction from our material toward establishing the etiology of chronic arthritis and acute rheumatic fever and toward differentiating the two conditions.

Material and Methods. During the past year the many patients with chronic arthritis coming to our outpatient department for intravenous

streptococcic vaccine treatment have had their serums tested routinely for streptococcic agglutinins before treatment was begun. The streptococcic agglutination titer was determined in 300. The serums of 66 patients with acute rheumatic fever—mostly children under 10 years of age—were also tested for streptococcic agglutinins. Children were chosen in order that there might not be any confusion in diagnosis between acute rheumatic fever and chronic arthritis. It was found in controls that the age had little significance in the height of agglutination titers.

As a comparison, the serums of 110 normal individuals, 46 cases of scarlet fever, and 20 patients with glomerulonephritis were also tested for streptococcic agglutinins. The normal persons were used for controls, and the cases of scarlet fever and glomerulonephritis were included because they are quite generally considered to be due to a streptococcic infection.

We attempted to see if the findings in our material supported the belief that, in most cases, chronic arthritis and acute rheumatic fever are of streptococcic origin and that they are produced by specific strains.

In making the agglutination tests two strains of streptococci were used. Strain 1, isolated from a patient having acute rheumatic fever, had been kept on media for 9 years. It produced a slight amount of green discoloration on sheep blood agar. It cross agglutinated in high dilutions (1 to 50,000) with most other strains of acute rheumatic and chronic arthritic origins with which it was tested. The second strain, from a case of chronic arthritis, hemolyzed blood slightly at times, but was generally a methemoglobin producer. It cross agglutinated (1 to 50,000) with the rheumatic organism and with most of the methemoglobin producing strains of chronic arthritic origin with which it was tested.

Strain 2 was not used in as many tests as Strain 1 but in a sufficient number to give a fair comparison of the two strains. Both were especially suited for use, since at 37° C. they grew in a fine homogeneous suspension in beef infusion broth (pH 7.6) and did not agglutinate spontaneously. They could be kept in a weak suspension in salt solution for 24 hours or more without settling out.

The suspensions for the agglutination tests were made from the sediments of a 24- to 48-hour broth culture in 0.9 per cent salt solution. This suspension was diluted so that, when mixed with an equal amount of the respective dilutions of the serums, a faint milkiness could be observed.

The blood for the tests was taken from a vein in the arm of the patient and stored in the ice box until the next day. The clear serum could then easily be pipetted off. The serums were diluted with salt solution as follows: 1 to 25, 1 to 50, 1 to 100, 1 to 200, 1 to 400, 1 to 800, 1 to 1600, 1 to 3200, etc. One cc. of each dilution was put into respective Wassermann tubes, and to each of the tubes was added 1 cc. of the suspension of streptococci, giving a total volume of 2 cc. in each tube. The final dilutions were twice those of the serums. The tubes were incubated in a water bath at 40° C. for 2 hours and then placed in the ice box until the next morning, when the agglutination titers were read.

The results of the agglutination tests from the groups described above are given in the following tables and descriptions. The significant differences of the statistics in the tables were checked by Pearson's Chi square formula and found to be significant.

Streptococcic Agglutination Titers in Normal Persons. The streptococcic agglutination titers were determined in 110 normal individuals with Strain 1 and in 81 with Strain 2 (Table 1). With Strain 1 the greatest number had a maximum agglutination titer

of 1 to 200. Thirty-two per cent agglutinated in dilutions above 1 to 200, but none of the 110 cases had titers above 1 to 800.

TABLE 1.—MAXIMUM STREPTOCOCCIC AGGLUTINATION TITERS. NORMAL PERSONS.

Dilutions.	Below 1 to 50.	1 to 50.	1 to 100.	1 to 200.	1 to 400.	1 to 800.	1 to 1600.	1 to 3200.	1 to 6400.	1 to 12,800.	1 to 25,000.	
Rheumatic strain, 110 cases	5.5%	15.5%	20%	27%	21%	11%	0	0	0	0	0	Above 1 to 200, 32%.
Chronic arthritic strain, 81 cases	2%	5%	2%	18.5%	44%	26%	2%	0	0	0	0	Above 1 to 400, 28%.

With Strain 2 the greatest number showed the highest agglutination at the dilution of 1 to 400; 28 per cent had titers above 1 to 400. The highest titer was 1 to 1600, at which level 2 per cent agglutinated. Strain 2 showed streptococcic agglutination in normal persons in slightly higher dilutions than Strain 1. Strain 2 appeared to be more sensitive to agglutination than Strain 1.

Streptococcic Agglutination Titers in Patients with Chronic Arthritis. The serums of 300 patients with chronic arthritis were tested for streptococcic agglutinins with Strain 1, and 60 cases with Strain 2 (Table 2). With Strain 1 the greatest number agglutinated at the dilution of 1 to 200, the same as with normal persons; 33 per cent agglutinated above 1 to 200. The titers in chronic arthritis with Strain 1 were not higher than in normal individuals.

TABLE 2.—MAXIMUM STREPTOCOCCIC AGGLUTINATION TITERS. CHRONIC ARTHRITIS.

Dilutions.	Below 1 to 50.	1 to 50.	1. to 100.	1 to 200.	1 to 400.	1 to 800.	1 to 1600.	1 to 3200.	1 to 6400.	1 to 12,800.	1 to 25,000.	
Rheumatic strain, 300 cases	10%	11%	22%	24%	21%	9%	2%	1%	0	0	0	Above 1 to 200, 33%.
Chronic arthritic strain, 60 cases	0	0	1.5%	7%	32%	38%	10%	10%	1.5%	0	0	Above 1 to 400, 59.5%.

The highest percentage of the 60 cases showed agglutinins with Strain 2 in the dilution of 1 to 800; 60 per cent agglutinated above 1 to 400, which was the peak of agglutination of normal persons with Strain 2. The group of chronic arthritic patients had higher titers with Strain 2 than was found in normal persons with this strain.

Streptococcic Agglutination Titers in Patients with Acute Rheumatic Fever. The agglutination titers were determined in 66 cases of acute rheumatic fever with both of the strains of streptococci (Table 3). The greatest number with Strain 1 agglutinated at 1 to 800; 48 per cent agglutinated in dilutions above 1 to 200, the peak of normal agglutination with Strain 1. The titers of rheumatic patients with Strain 1 were higher than was found with this strain in normal individuals.

TABLE 3.—MAXIMUM STREPTOCOCCIC AGGLUTINATION TITERS. ACUTE RHEUMATIC FEVER.

Dilutions.	Below 1 to 50.	1 to 50.	1 to 100.	1 to 200.	1 to 400.	1 to 800.	1 to 1600.	1 to 3200.	1 to 6400.	1 to 12,800.	1 to 25,000.	
Rheumatic strain, 66 cases	12.5	9%	9%	21%	13.5%	23%	8%	3%	1%	0	0	Above 1 to 200, 48.5%.
Chronic arthritic strain, 66 cases	0	0	3.5%	0	7%	17%	7%	38%	17%	10%	0	Above 1 to 400, 89%.

The greatest percentage of the cases with Strain 2 had maximum agglutination titers at 1 to 3200; 17 per cent agglutinated at 1 to 6400 and 10 per cent at 1 to 12,800; 89 per cent showed agglutination in dilutions above 1 to 400, as compared with 28 per cent in normal persons with the same strain. It is evident that serums of patients having acute rheumatic fever have streptococcic agglutinins in much higher dilutions than the serums of normal persons. It is also seen that the serums of patients with acute rheumatic fever agglutinate in higher dilutions with the strain from chronic arthritis than with that from acute rheumatic fever.

As controls the serums of 46 persons with scarlet fever (Table 4) and 20 with glomerulonephritis (Table 5) were also tested for agglutinins for the rheumatic and the chronic arthritic strains. With Strain 1 the greatest number of the serums of scarlet fever cases agglutinated at the dilution of 1 to 800. The percentage agglutinating above 1 to 200 (the normal peak) was 86. The highest point of agglutination with Strain 2 was at the dilution of 1 to 6400; 90

TABLE 4.—MAXIMUM STREPTOCOCCIC AGGLUTINATION TITERS. SCARLET FEVER.

Dilutions.	Below 1 to 50.	1 to 50.	1 to 100.	1 to 200.	1 to 400.	1 to 800.	1 to 1600.	1 to 3200.	1 to 6400.	1 to 12,800.	1 to 25,000.	
Rheumatic strain, 46 cases	0	0	4%	9%	13%	28%	19.5%	15%	9%	2%	0	Above 1 to 200, 86.5%.
Chronic arthritic strain, 46 cases	4	0	0	4%	2%	9%	17%	19.5%	33%	9%	2%	Above 1 to 400, 89.5%.

TABLE 5.—MAXIMUM STREPTOCOCCIC AGGLUTINATION TITERS. GLOMERULONEPHRITIS.

Dilutions.	Below 1 to 50.	1 to 50.	1 to 100.	1 to 200.	1 to 400.	1 to 800.	1 to 1600.	1 to 3200.	1 to 6400.	1 to 12,800.	1 to 25,000.	
Rheumatic strain, 20 cases	0	0	0	0	0	25%	45%	5%	20%	5%	0	Above 1 to 200, 100%.
Chronic arthritic strain, 20 cases	0	0	0	0	0	0	15%	15%	40%	30%	0	Above 1 to 400, 100%.

per cent agglutinated above the dilution of 1 to 400 (the normal peak).

The most common point at which agglutination took place with Strain 1 in the 20 serums from glomerulonephritis was at the dilution of 1 to 1600. All agglutinated in dilutions above the normal peak for this strain. With Strain 2 the greatest percentage of cases showed agglutination in the dilution of 1 to 12,800. All agglutinated in dilutions above the normal for this strain.

Comment and Summary. Streptococcic agglutination titers were determined in chronic arthritic and acute rheumatic fever patients for two strains of streptococci. The first strain was isolated from a case of acute rheumatic fever and the second from a case of chronic arthritis.

Comparing the agglutination titers of the above conditions with those of normal persons and of patients with scarlet fever and glomerulonephritis, with the rheumatic strain the agglutination titers of acute rheumatic patients were higher than normal, while those of the chronic arthritic patients were not. With the chronic arthritic strain the titers were higher than normal in both chronic arthritis and acute rheumatic fever, but higher in the latter. With both strains the titers were decidedly higher than normal in both scarlet fever and glomerulonephritis. In all tests, including the normal serums, the chronic arthritic strain was agglutinated in higher dilutions than the acute rheumatic strain. The chronic arthritic strain appeared to be more sensitive to agglutination.

These findings suggest that both chronic arthritis and acute rheumatic fever are streptococcic infections. The view that chronic arthritis is due to a specific strain is not supported, since the chronic arthritic strain was agglutinated in higher dilutions with serums from acute rheumatic fever patients than with the serums of patients with chronic arthritis. The lack of strain specificity is also shown by the fact that both the rheumatic and the arthritic strains were agglutinated in higher dilutions with serums from scarlet fever and glomerulonephritis than with the serums from acute rheumatic fever or chronic arthritis.

Summary. The streptococcic agglutination tests in these series suggest that both chronic arthritis and acute rheumatic fever are due to a streptococcic infection, but that neither of these diseases is produced by a specific strain of streptococcus.

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MONOCYTIC LEUKEMIA WITH DATA ON THE INDIVIDUALITY AND DEVELOPMENT OF THE MONOCYTE.

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Until recently hematologists have not recognized monocytic leukemia as a separate leukemic blood picture. (See Dameshek's[3] review of 18 definite cases.) All cases have had a gradual onset of fatigue, swollen gums and fever, and a rapid course of a few weeks to a fatal termination. Postmortem examination has revealed the lymph nodes, spleen and bone marrow crowded with mononuclear cells; this has been interpreted as a proliferation of the reticulo-endothelial system. A similar case, whose blood picture and progressive changes tends to clarify the nature of this entity, is the subject of this report.

Case Report. The patient, a male physician, aged 55 years, was admitted to the University Hospital on June 23, 1931, complaining of weakness and fever.

On February 1, 1931, the patient was confined to bed for 2 weeks with fever mounting to 104° F., five chills and general malaise. The fever abated and the patient felt better, but remained weak and noticed dyspnea on exertion. About 20 weeks later (June 16, 1931) his temperature rose to 103° F. following treatment for pyorrhea alveolaris, with exacerbation of his weakness and general debility, hoarseness and nocturia.

He had had the usual childhood exanthemata, and had pyorrhea for about 20 years. Several years previously he was treated for furunculosis with bacteriophage.

Physical examination showed a pale white man appearing older than his years. The conjunctiva and pharynx were injected. There was marked recession of the gums and moderate enlargement and tenderness of the submaxillary lymph nodes. A few coarse râles were heard in both lung bases posteriorly. The heart was normal in size, sounds and rate (90 per minute). The blood pressure was 120 systolic and 68 diastolic. There was no general glandular enlargement. The liver and spleen were not palpable.

The blood examination showed: hemoglobin, 50 per cent (Sahli); red blood cells, 2,480,000 per c.mm.; white blood cells, 50,000 per c.mm.; differential: polymorphonuclear neutrophils, 8 per cent; "blasts," 4.3 per cent; lymphocytes, 6.3 per cent; monocytes, 80 per cent. Many pale macrocytes were present. The platelets were scarce and a few giant forms were present.

The patient was observed for 1 day and then returned to his home for 9 days. During this period he used Fowler's solution in increasing doses, reaching 27 drops a day. His weakness on returning to the hospital was profound. He had been nauseated and had vomited on two occasions. He had a continuous headache and his temperature had reached 102° F.

every evening. Examination now (July 3, 1931) revealed: ulceration of the gums opposite the first right upper and lower bicuspid teeth following treatment of his pyorrhea with caustics; pulse, 110; respiration, 28 per minute; temperature, 103° F.; soft apical systolic murmur. Blood count: hemoglobin, 38 per cent (Sahli); red blood cells, 1,300,000 per c.mm.; white blood cells, 20,500 per c.mm.; differential: polymorphonuclear neutrophils, 11 per cent; "blasts," 3 per cent; lymphocytes, 17 per cent; monocytes, 69 per cent. The red blood cells were well colored and normal in size. The platelets were plentiful. Other laboratory findings at this time were: Kahn test negative. Agglutination for Brucella melitensis positive in dilution of 1 to 60; for Brucella abortus, Bacillus typhosus and paratyphosus A and B negative. Blood culture negative. Blood Group IV (Moss). The urine contained a trace of albumin, no sugar, no bile or increase in urobilinogen, occasional white blood cells, no red blood cells or casts. Stool: no occult blood. No Vincent's organisms were found in smears made from the ulcerations in the gums.

Course. The patient was kept in bed, and sedatives and mild antiseptic mouthwashes were given. He received five blood transfusions of 500 cc. each on July 5, 7, 11, 17 and 30. Following each transfusion there was subjective and objective improvement, although the ulcer in the mouth grew in size to occupy the right half of the palate and showed no signs of granulation tissue until July 13, 14 days after its appearance. By July 15 the patient was sufficiently improved to get up a short period each day. About this time, 24 weeks after onset, the spleen became palpable (2 fingerbreadths), but there was no tenderness. The liver edge was barely palpable. The blood picture showed a progressive change to July 22, 25 weeks after onset, when the count was: hemoglobin, 65 per cent (Sahli); red blood cells, 3,200,000 per c.mm.; white blood cells, 14,050 per c.mm.; differential: polymorphonuclear neutrophils, 45 per cent; "blasts," 8 per cent; lymphocytes, 33 per cent; monocytes, 14 per cent. Seven days later (July 29) a new turn in the blood picture appeared. The white blood cells increased to 24,200 per c.mm. The differential count showed: polymorphonuclear neutrophils, 26 per cent; "blasts," 47 per cent; lymphocytes, 21 per cent; monocytes, 6 per cent. At this time the patient complained that he again felt as he had at the onset of his illness, 27 weeks previously. Because many teeth were almost falling out and were exquisitely tender, those in the right upper jaw surrounding the area of necrosis were extracted on August 1, 1931, without any unusual hemorrhage resulting. In view of the reduction in the white blood cell count which occurred following the use of Fowler's solution at the time of his first admission, this was again tried.

The white blood cell count rapidly rose in a week's time from 24,200 to 155,000 per c.mm., with exacerbation of symptoms which had begun to recur the previous week associated with the increase in the number of leukoblasts in his blood. He was again confined to bed, his temperature went as high as 103° F. in the evenings and he had mild chills and drenching sweats each night. He complained of headache and oozing from his gums. He had no appetite and was nauseated and vomited on several occasions. He attributed this to the arsenic medication, although he had taken a total of only 60 drops of Fowler's solution. He now had a "catch" in his left side. Physical examination, 27 weeks after onset, showed: dyspnea, pallor, skin hot and dry, necrosis of the palate as before, gums swollen, red and oozing blood, spleen palpable (3 fingerbreadths) and tender, and slight abdominal distention.

The temperature rose as high as 104° F. with frequent chills. Blood transfusions were given on August 10 and 13 and Roentgen ray radiation was applied to the mouth, spleen and long bones on the latter date. On

August 13 purpuric spots appeared over the shoulders, bleeding from the gums became continuous and the white blood cell count increased to 210,000 per c.mm. Gross hematuria occurred on August 14 and the patient expired the same evening following 1 hour in coma with Kussmaul respiration, 28 weeks after the onset of his illness. Permission for postmortem examination was not granted.

The clinical condition during the patient's stay in the University Hospital can easily be divided into four stages: (1) That on admission, 21 weeks after onset; (2) a remission following transfusions, 24 weeks after onset; (3) an exacerbation starting 25 weeks after onset; (4) a terminal stage, 27 weeks after onset. At the beginning of this patient's illness the clinical picture was essentially the same as in the first stage, described above, 21 weeks after the appearance of symptoms.

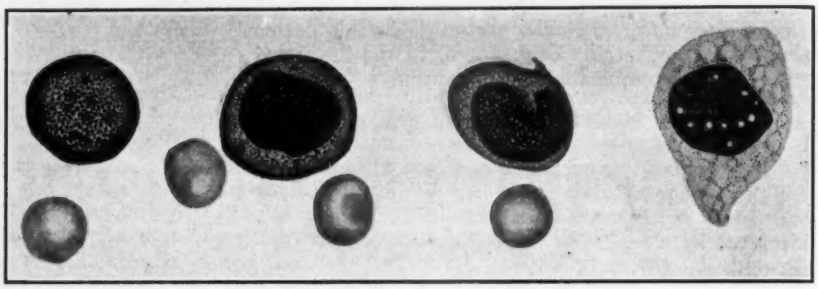
TABLE 1.—THE BLOOD PICTURE.

Date, 1931.	Hemoglobin, per cent.	R.b.c., millions.	W.b.c., thousands.	Pmn., per cent.	Eos., per cent.	Bas., per cent.	"Blast," per cent.	Sm. Ly., per cent.	L. Ly., per cent.	M., per cent.	H., per cent.
June 23	50	2.3	50.0	8	0.7	0.3	0	3	3	80	4.3
July 3	38	1.3	20.5	11	0	0	3	17	0	69	3
4	..	..	16.0								
5	Transfusion										
6	40	1.7	20.2	10	0	0	0	11	0	80	0
7	Transfusion										
9	50	2.2	15.1								
10	55	2.4	11.4	40	1	1	5	22	3	28	2
11	Transfusion										
14	75	3.4	14.0	38	1	1	8	21	9	22	0
16	65	2.6	15.9	41	0.5	0.5	1	28	0	29	0
17	Transfusion										
19	65	3.0	17.5	37	0	0	5	25	5	30	0
22	65	3.2	14.0	45	0	0	8	18	15	14	0
25	75	2.9	16.7	41	0	0	20	32	0	7	0
29	70	3.3	24.2	26	0	0	47	20	1	4	2
31	Transfusion										
Aug. 3	65	3.0	58.2	20	0	0	46	16	6	10	2
4	..	..	61.0								
6	65	2.6	60.0								
9	58	2.9	135.0	3	0	0	86	2	0	0	9
11	..	..	155.0								
12	Transfusion										
13	..	..	210.0	1	0	0	86	3	2	3	5
	Transfusion and Roentgen ray										
14	Death										

The Blood. During the patient's residence in the hospital the identification of the white blood cells in making the differential count on Wright-stained smears was aided by the Goodpasture[1] peroxidase technique and the vital staining methods of Sabin.[2]

The type cell of the blood film on first admission to the hospital—the mature monocyte—was a large oval cell, about 20 by 30 microns in size, which often showed little outpouchings of clear cytoplasm. The cytoplasm had a pale, gray-blue, foamy appearance and was dusted with azure granules which varied greatly in size. Many of these cells contained large vacuoles. The nucleus was round, horseshoe-shaped or convoluted, and stained a dark

violet. The chromatin network was very fine and there were no nucleoli. (Fig. 1, *C*.) Some of the monocytes were of the so-called transitional type, but the majority contained large round or oval nuclei. The peroxidase stain gave either a negative or faintly positive reaction in these cells. These cells in vital stained preparations showed neutral red granules collected in the "hof" of the nucleus and the cells had the characteristic sluggish lateral motility of the monocyte. A few histiocytes were present in the early smears and occasional leukoblasts were seen.



A *B* *C* *D*

FIG. 1.—Cells from the peripheral blood. (*A*) Monocyte blast; (*B*) young monocyte; (*C*) mature monocyte; (*D*) hemohistioblast of the monocyte series. The red blood cells give comparison for the size of the cells. (Wright stain.)

As the chart shows, the number of mature monocytes gradually decreased, approaching normal absolute number, as the patient enjoyed a remission. Toward the end of this remission a younger type of cell began to appear in increasing numbers. These cells are charted as "blasts." These earlier forms were cells about 20 microns in diameter. With vital stains they were nonmotile and assumed a round or slightly oval shape containing a large round or kidney-shaped nucleus which nearly filled the cell. Nucleoli, which moved about the nucleus, could often be seen. In some of these cells large dancing cytoplasmic granules lying in the concavity of the kidney-shaped nucleus collected the neutral red stain. Most of them, however, did not contain neutral red granules. These cells did not take the peroxidase stain. In the Wright-stained preparations the cell was about 20 microns in diameter and nearly round. The large nucleus that nearly filled the cell was round, oval or indented. The fine chromatin network stained a light reddish purple and there were 2 to 4 indistinct blue-staining nucleoli. The scanty cytoplasm stained a deep, coarse ultramarine blue and there were no granules. (Fig. 1, *B*.)

Histiocytes were seen in nearly every smear. Several were observed under vital staining conditions. These were enormous cells in the neighborhood of 40 microns in diameter which were very actively motile, moving across an oil-immersion field in a couple of minutes. They had clear cytoplasm containing a few large Janus green granules and a small solid homogeneous-appearing nucleus which was about 10 microns in diameter. Dameshek[4] has very well described this cell in the Wright-stained smear as a very large and irregularly shaped cell with a sky-blue cytoplasm containing vacuoles and coarse azure granules. The nucleus takes a red-purple stain and has a spongy appearance. There are several distinct blue-staining nucleoli. The peroxidase reaction is negative. (Fig. 1, *D*.)

The terminal stage began 27 weeks after onset with a very primitive cell in the blood films. These primitive cells made up 86 per cent of the 210,000 white blood cells per c.mm. on August 13. These cells were round or oval,

varying from 15 to 40 microns in size, with large, round, oval or indented nuclei that nearly filled the cell. The cytoplasm was very dark blue and coarse without granules. The nucleus had a very indistinct nuclear margin; the fine granular chromatin stained a faint lavender and there were several indistinct blue-staining nucleoli. (Fig. 1, *A*.) These cells were nonmotile. None of these cells absorbed the neutral red dye. The appearance in supravital stained preparations of these primitive cells and of the young monocytes present in the preceding phase of the disease is identical with that described by Forkner[7] for the monoblasts and the premonocytes which he observed in the lymph nodes of intravitally stained rabbits. The peroxidase reaction of these primitive cells was only rarely faintly positive. Several dividing cells and cells containing mitotic figures were seen. A few histiocytes were present.

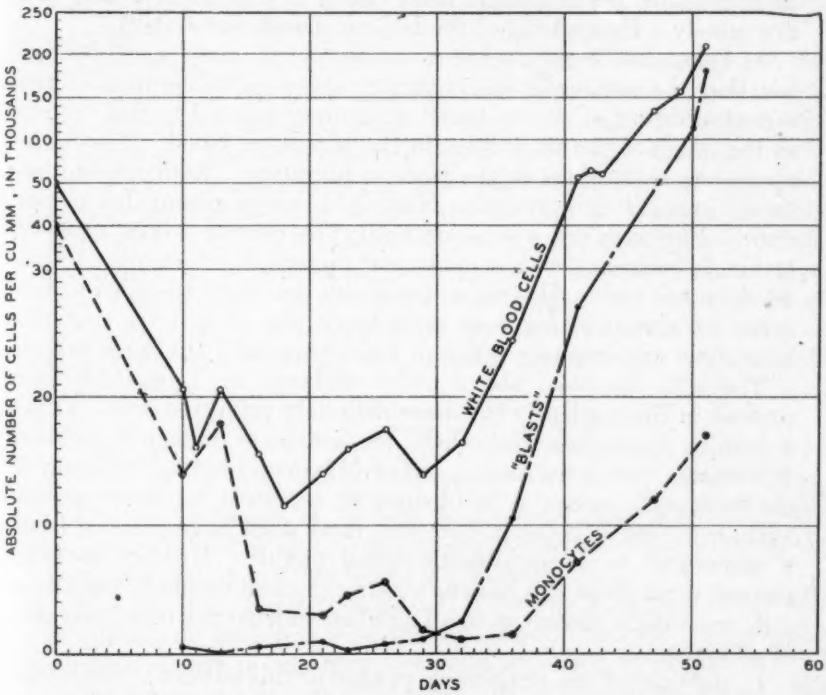


CHART I.—THE COURSE OF TOTAL LEUKOCYTES, "BLASTS" AND MONOCYTES.

Comment. What are these primitive cells? Dr. Isaacs has described these cells and the changes which took place in the character of the monocytes in this patient's blood and pointed out the differences between these primitive cells and the myeloblasts and the lymphoblasts: "These cells which resemble myeloblasts differ from them in several respects. The chromatin in the nucleus of the cells which have been stained with Wright's stain has coagulated into fine granular masses instead of the reticular type of the myeloblast or the coarsely granular type of the lymphoblast. There is no

sharply defined nuclear membrane. The cells contain multiple nucleoli. The cytoplasm stains a deep blue, and is coagulated into coarse masses. No definite granules are evident. The cell is a monocyte blast. (Fig. 1, *A*.) All gradations from this cell to the young monocyte and the adult forms can be found in the films. (Fig. 1, *A, B, C*.) The predominant cell in the early stages of the disease was the mature monocyte (transitional cell) with an indented nucleus and foamy blue cytoplasm. (Fig. 1, *C*.) As the disease progressed the more immature forms became more numerous, until at the time of death the blast stages were very common. We have here, then, a typical 'shift to the left' in the development of the monocytes, to the monocyte blast (which is a distinctive cell) and not merely a hyperplasia of the reticuloendothelial system."

As Dameshek's[3] review brings out very well, many authors have felt that the monocytic blood picture and the proliferation of the reticuloendothelial system found at autopsy pointed to this system as the origin of the monocytes in the peripheral blood. The name applied to these cases in the German literature, "Reticuloendotheliose," indicates this attitude. Naegeli,[4] however, claims that monocytic leukemia is not a separate entity; he records several cases of leukemia beginning with a monocytic picture which changes into a myeloblastic type. He further maintains that these so-called monocytes are abnormal forms of myeloblasts, for he believes that the monocytic and granular series of leukocytes have the same origin.

The cells described above which replaced the monocytes first present in this patient's blood are definitely primitive cells. If, as is held by Dameshek[3] and others, the histiocyte (hematohistioblast of Ferrata, resting wandering cell of Maximow) is the precursor of the monocytic series, it is obvious to conclude, as have several authors as well as Naegeli, that such cases must have changed from a monocytic to a myeloblastic blood picture. Histiocytes were present throughout this patient's course in small numbers, but these cells are usually present in small numbers in leukemic blood pictures of all types.

In the light of the progressive change in this patient's blood cells from the mature monocyte through a stage of younger cells to a very primitive blast, and the definite differences in morphology and staining characteristics which Dr. Isaacs has pointed out between this primitive blast and the myeloblast, we feel that this case demonstrates the existence of a definite cell series separate from the granulocyte series and the reticuloendothelial system. Such a conception explains the apparent incongruity of Naegeli's[4] cases, which changed from a monocytic to a blastic blood picture. Furthermore, consideration of the autopsy protocols describing proliferation of the reticuloendothelial system leaves considerable doubt in mind of such an interpretation. For instance, Wyschegorodzewa's[5] description of cells of myeloblast type in the microscopic appearance of

the bone marrow, spleen and lymph nodes in a case of monocytic leukemia makes it difficult to connect these cells with reticular tissue.

"The reticulum (of the bone marrow) is poorly developed. The whole space between its meshes is filled with large cells with vesicular, round, oval or kidney-shaped nuclei with one or more nucleoli and small masses of basophilic staining nongranular cytoplasm. Among these cells are distributed cells with dark nuclei and more basophilic cytoplasm. It is impossible to connect these cells with the reticular tissue. . . . In the spleen . . . the lymphoid tissue is crowded with pale large vesicular cells which are analogous to the cells in the bone marrow. In the lymph nodes . . . are cells in large numbers of the type present in the spleen and bone marrow . . . of the type of the myeloblast."

Most reports also call attention to the absence of changes in the Kupffer cells of the liver sinusoids—one of the definite portions of the reticuloendothelial system. Naegeli's attempt to divide cases of monocytic leukemia into two types—those with and those without myeloid metaplasia of the bone marrow—is interesting in this connection. It seems to us that the findings in this case are more compatible with an acute and a chronic stage of monocytic leukemia analogous to the chronic myeloid and acute myeloblastic forms of myeloid leukemia. Wyschegorodzewa[5] reports interesting findings in bone-marrow punctures done on the case of monocytic leukemia mentioned above during a remission and during the terminal exacerbation:

	Myeloblasts, per cent.	Monocytes, per cent.	
VIII. 23	2.6	73.2	Remission.
IX. 23	73.2	0.4	Terminal.

The predominance of "blasts" in the bone marrow as well as the peripheral blood stream characterizes the acute stage of monocytic leukemia just as in other forms of leukemia.

The excellent colored plates and descriptions of cells in the case of monocytic leukemia reported by Swirtschewskaja[6] show a progressive change in cells from normally appearing monocyte to a cell in the terminal stage which appears like our monocyte blast. The postmortem findings in this case are very similar to those of Wyschegorodzewa,[5] although from the published microphotographs it appears to us that undue stress is laid on the irregularity of the endothelial lining of the splenic sinuses.

Summary. 1. This is a case of monocytic leukemia which began with malaise, fever, chills, weakness and gingivitis. A period of marked improvement with residual weakness followed. The patient was first seen during his second exacerbation of symptoms when a necrotic stomatitis developed. Following several transfusions a second remission occurred. A third exacerbation of symptoms followed which rapidly progressed to a fatal terminal condition 28 weeks after the onset of the disease.

2. The blood picture changed from one with 40,000 mature monocytes (transitional forms) per c.mm. through a stage of symptomatic remission in which the white blood count reached a normal level and the differential count revealed the round nucleus type of mature monocyte in normal numbers. Before the rise in the white blood count with the third exacerbation of symptoms a less differentiated type of monocyte appeared in the blood films in increasing numbers. Immature monocytes rapidly increased in numbers and immaturity until the terminal blood film showed 180,000 primitive blasts per c.mm.—the monocyte blast—whose appearance and characteristics are different from those of the myeloblast and the lymphoblast.

3. The progressive changes in the maturity of the monocytes in this patient's blood demonstrate a third definite leukocyte series—mature monocyte, young monocyte, monocyte blast—which does not involve the reticuloendothelial system.*

NOTE.—The authors wish to express their appreciation to Dr. Raphael Isaacs for his stimulating interest and guidance in the study of this patient.

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ACUTE MONOCYTIC LEUKEMIA. A CASE WITH PARTIAL AUTOPSY.†

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SINCE Reschad and Schilling-Torgau's[1] description in 1913 of acute leukemia with the monocyte as the type cell, reports of some

* The hematologic data in this case would seem to support more convincingly the belief in the existence of a third leukocytic series than that this series does not involve the reticuloendothelial system.—EDITOR'S NOTE.

† Although the cases described in this and the preceding paper are apparently of the same nature, it will be seen that a different origin for the cell concerned is suggested by the respective authors. It is felt that this juxtaposition of the two points of view should be valuable to our readers.—EDITOR'S NOTE.

28 cases have appeared under the titles "Monocytic Leukemia"[2–12,18], "Reticuloendotheliosis"[13–16] and "Hemohistioblastic Syndrome."[17] Of these only 17 have been so fully described as to appear convincing. The observations in an additional case are presented.

Case Report. Mrs. L. B. Case 71584, a white woman, aged 47 years, was admitted to the University Hospital on January 18, 1931, complaining of weakness, swelling of the left ear and an abscess over the coccyx. She gave a history of measles, scarlet fever, mumps and whooping cough during childhood. Her two pregnancies had terminated in spontaneous abortions during the third month. She had suffered from pyorrhea for 5 years. Her husband died in 1918 of pulmonary tuberculosis. She dated her present illness from November 15, 1930, when she noticed many pale bluish spots over her thighs and legs, at the time attaching no significance to them, attributing them to insect bites. On December 3 following exposure to cold she developed a severe sore throat with swelling of the glands in the left side of the neck; this lasted only 3 days. Approximately 1 week later she noticed tenderness and swelling over the coccyx followed in a few days by the development of an abscess. From December 15 she felt weak and ill and was dyspneic on exertion. There were recurrent crops of bluish spots on the skin of the body, arms and thighs. On January 3 the right upper premolar tooth was extracted on account of acute toothache and was found to be "abscessed;" following this the gums became tender and bled easily. On January 8 her left ear developed a marked painless swelling, so that hearing was impaired by closure of the external canal. On January 15 a furuncle developed in the left axilla. The discomfort occasioned by this and by her weakness caused her to enter the hospital.

Physical Examination. A strikingly pale, slightly dyspneic woman well developed and well nourished. Her temperature was 101.6° F; pulse, 100; respirations, 22. Scattered thickly over the trunk and thighs and more sparsely over the legs were innumerable purplish macules, varying from 1 mm. to 1 cm. in diameter. On both arms were remarkable annular purpuric lesions, from 2 to 3 cm. in diameter; over the extensor surfaces of the forearms these were confluent. In addition to the fresh petechiæ, there were numerous light brown stains of a previous eruption. There was no jaundice. The ankles showed slight pitting edema.

The head and sinuses were negative. The left auricle was of approximately twice normal size, thick, pale, indurated, not tender; the auditory meatus was reduced to a slit plugged with cerumen. The right ear was negative on external and otoscopic examination. The eyes presented nothing remarkable, even on ophthalmoscopic examination. The nose showed no abnormalities. The buccal mucosa was pale, the gums spongy and slightly swollen with a small superficial ulceration at the base of the lower left lateral incisor. Several teeth were missing, many were filled. The tongue was pale, coated and tremulous. The tonsils were small and pale and no pus could be expressed. The thyroid gland was normal in size and consistency. The posterior cervical lymph nodes on the left side were moderately enlarged and firm as were the inguinal glands; there was no general adenopathy.

The thorax and lungs were negative in all respects. The heart was normal and the sounds of good quality, except for soft short systolic bruits at the mitral and pulmonic areas. The heart rate was increased. The peripheral arteries felt soft. The blood pressure was 120 systolic and 100 diastolic.

The abdomen was flat; there was no lateral bulging; there was the old

scar of a McBurney incision. The liver was slightly enlarged (from fifth rib to 4 cm. below the costal margin). The spleen could not be felt, although the area of splenic dullness was thought to be moderately increased. The kidneys were apparently normal. There was no evidence of free peritoneal fluid.

The external genitalia showed marked edema of the labia minora and a small amount of thick, yellow vaginal discharge. Over the tip of the coccyx was a resolving furuncle. Rectal examination was negative.

The extremities were negative, except for the eruption and edema described. In the left axilla was a small furuncle and the adjacent axillary lymph nodes were moderately enlarged. The reflexes were normal.

Laboratory Examinations. The blood showed 55 per cent hemoglobin (Sahli); 2,960,000 erythrocytes; color index, 0.9; 150,000 platelets and 71,500 leukocytes per c.mm.; neutrophils, 2.7 per cent; eosinophils, 0.1 per cent; basophils, *nil;* myelocytes, 0.2 per cent; myeloblasts, 0.2 per cent; lymphocytes, 11.4 per cent; monocytes, 81.8 per cent; "immature" cells, 3.2 per cent; smudges, 1.4 per cent (500 cells, Jenner-Giemsa stain). The predominating cells were monocytes of the type ordinarily seen in normal blood: Large cells, from 12 to 20 microns in diameter, with abundant gray-blue spongy cytoplasm, irregular fine azure granulation and occasional vacuoles. The nuclei stained purple, with the exceptions noted below, and were rather coarsely reticulated with definite marginal condensation of the chromatin and no nucleoli. Some 35 per cent of these cells contained round or oval nuclei; of these the majority exhibited typical morphology and color. A small percentage had nuclei which were slightly larger and which stained violet rather than purple; the chromatin network was finer and there were occasional nucleoli. The remaining 65 per cent of monocytes had lobed or convoluted nuclei of varying complexity but with typical reticulation and no nucleoli. Very many of the cells of both groups were irregular in shape, elongated, "tailed" or with marked peripheral budding. The 3.2 per cent of cells classified as "immature" were believed to be young monocytes. These were large cells, 15 to 40 microns in diameter, quite irregular in outline, some round, some oval, many bizarre in shape with buds, pseudopodia and elongated streamers of cytoplasm. The cytoplasm was abundant, definitely reticulated or spongy, gray-blue, taking a more basophilic stain than the mature monocytes. Azure granulation was infrequent and, when present, the granules were massed near the nucleus, usually in clumps on opposite sides of the cell leaving the periphery ungranulated. A small number of the round and oval cells contained Auer bodies, and in some instances these seemed to be breaking up into azure granules. The nuclei were large, violet staining, round or oval and frequently eccentrically placed. The reticulum was extremely fine, giving a homogeneous appearance quite different from the even stippling of the myeloblastic nucleus; there was definite peripheral condensation of the chromatin and 1 to 3 nuclei were quite regularly present. In many of the larger cells the nuclei showed several or many buds; this phenomenon seemed not to be associated with mitosis.

The neutrophils showed no noteworthy abnormalities. The occasional myeloblasts and myelocytes were quite typical in form and tinctorial reactions. The lymphocytes were largely of the small type. Very rarely a large oval deeply basophilic plasma cell was seen.

Peroxidase stains (Goodpasture) showed that 67 per cent of the monocytic cells were oxidase negative and 33 per cent positive; the reacting granules were scanty and exceedingly small.

With supravital staining by Sabin's method the cells classified as monocytes reacted typically; neutral red appeared in fine granules clustered near the nuclear incisures of cells with lobulated nuclei and scattered through

FIG. 1.—Group of mature monocytic cells showing strikingly irregular outlines. (× 900.)

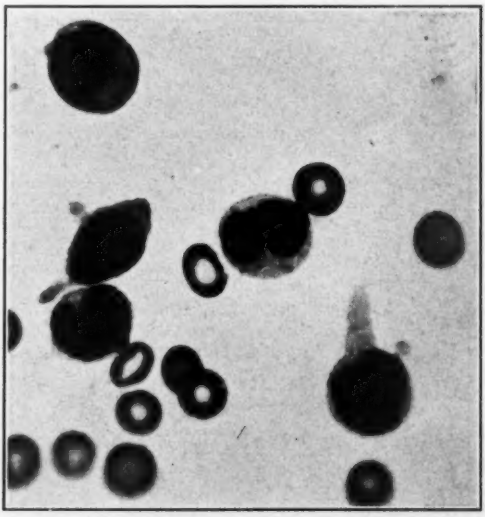

FIG. 2.—Tailed or racquet forms. Immature monocyte with Auer bodies at upper left of field. (× 1250.)

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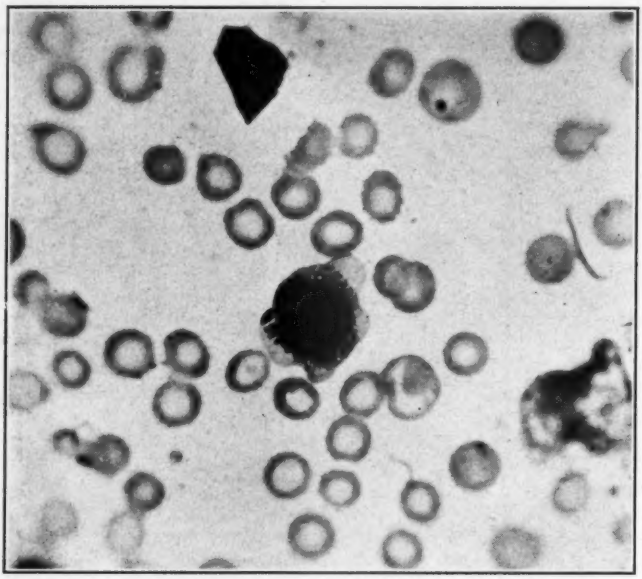

FIG. 3.—Immature monocyte with nuclear excrescences. (× 1250.)

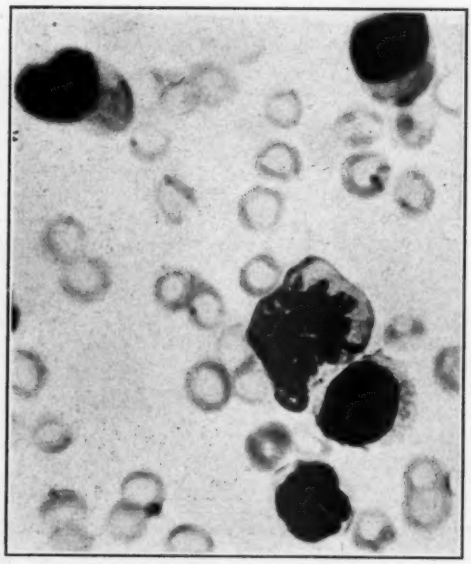

FIG. 4.—Mitotic form. (× 1250.)

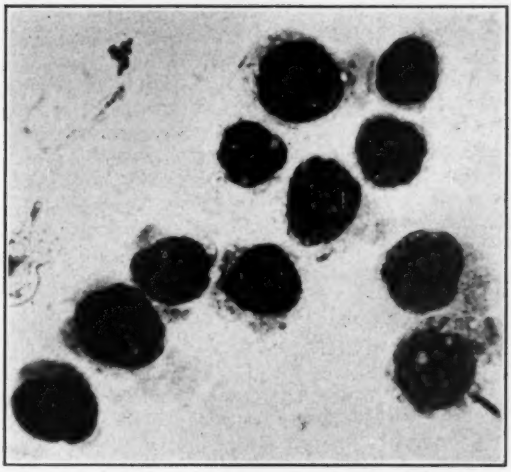

FIG. 5.—Smear from bone marrow. (× 1250.)

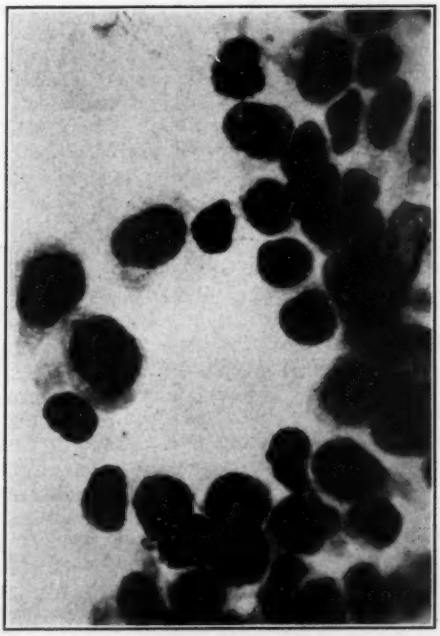

FIG. 6.—Smear from spleen. (× 1250.)

the cytoplasm of cells with round nuclei. Both types of cells were actively motile on the warm stage. The larger "immature" cells showed coarser granulation without tendency to clumping, motility was marked and it seemed that all gradations between them and typical monocytes could be seen. The picture of cellular motility presented by these preparations was in striking contrast to that of immobility seen in myeloblastic leukemia.

The erythrocytes presented little of note; there was slight anisocytosis and poikilocytosis with moderate central pallor. Many cells showed diffuse basophilia and there were a very few normoblasts; reticulocytes numbered 6 per cent (brilliant cresyl blue). The platelets were diminished in number and were mostly larger than normal. The bleeding time was 3 minutes (Duke's method); the coagulation time, 5 minutes (Lee's method). The red cells were normally resistant to hypotonic sodium chlorid solutions, hemolysis beginning at 0.42 per cent—complete at 0.2 per cent.

The blood glucose was 100 mg. per 100 cc.; the nonprotein nitrogen, 23 mg. There was no increase in bile pigment in the blood. The Wassermann reaction was weakly positive (2+) and the Kahn and Hinton tests strongly positive on 2 occasions. The urine was constantly of low specific gravity, contained traces of albumin and a few casts from time to time, usually in association with febrile exacerbations; 45 per cent of phenolsulphonephthalein was excreted during the test period. The sputum was negative for tubercle bacilli. The stools showed nothing of importance.

This patient remained in the hospital until her death on March 13, 1931. There was continuous elevation of temperature from 99° to 104° F., with an irregular diurnal variation. There were repeated eruptions of purpuric spots and, during the last 3 weeks of life, marked infiltration of the skin of the trunk and thighs. The spleen was never felt; the liver and lymph glands did not change in size. Blood cultures in various media taken on January 23 and 25 and February 15 remained sterile. A roentgenogram of the thorax made on February 5 showed no evidence of mediastinal or pulmonary infiltration. On account of progressive anemia transfusions of blood were given on February 11 and 18. Her condition failed rapidly, and after March 1 she was completely prostrated and almost constantly delirious. After March 3 there was a marked diminution in the amount of fever, her temperature never rising above 100. On March 11 a pleural friction was heard over the left back, and on the following day there were signs of a considerable accumulation of fluid. Death occurred on March 13; no autopsy was allowed, though permission was granted to remove a portion of a rib. Small specimens of skin and spleen were secured also and it was seen that the spleen was of approximately twice normal size.

The details of daily blood examination are shown in Table 1. Anemia became profound during the third week of observation, the hemoglobin falling to 15 per cent and the erythrocytes to 900,000; following transfusion there was some improvement which persisted for 2 weeks. There was never evidence of marked erythropoiesis, though the reticulocytes were constantly increased to 6 or 7 per cent. The number of leukocytes was exceedingly variable, wide fluctuations occurring from day to day. The count fell rapidly after admission, reaching 12,000 on January 28; from this date until February 25 there was at no time any marked leukocytosis, and on 1 day the count was 3500. After February 26 there was a rapid rise with variations between 20,000 and 60,000 leukocytes until the last few days of life when there was a sudden increase to over 100,000. During the entire period of observation there was a relative and absolute neutropenia and paucity also of other polymorphonuclear types. The lymphocytes showed a marked absolute increase though the relative percentage was at times low. Care was exercised to avoid confusing lymphocytes with micro-

myeloblasts and the counts were checked frequently with peroxidase and supravital stains. The total percentage of monocytic cells, combining mature and immature forms, varied from 49 to 93 per cent, remaining between 70 and 85 per cent during most of the observation period. In the last week of life the relative number of immature monocytic cells increased greatly; occasional mitotic figures were observed and in a few smears monocytes were seen which had phagocytosed erythrocytes; phagocytosis was not

TABLE 1.—DAILY BLOOD EXAMINATION. (DIFFERENTIAL COUNT, 500 CELLS, JENNER-GIEMSA STAIN.)

Date.	Hemoglobin, per cent.	Erythrocytes millions.	Leukocytes thousands.	Neutrophils.	Eosinophils.	Basophils.	Lymphocytes.	Monocytes.	Immature cells.	Myelocytes.	Myeloblasts.	Plasma.	Smudges.
Jan. 20	55	2.9	71.2	2.7	0.1	0	11.4	81.8	3.2	0.2	0.2	0	1.4
22	35	2.3	55.2	0.7	0	0	13.0	80.5	3.0	0	0.3	0	3.0
23	..	..	70.0	2.2	0	0	10.8	80.9	3.7	0	0.1	0	2.3
24	..	..	21.4	5.5	0	0	16.0	73.0	5.0	0	0.1	0	0.4
25	30	..	24.3	2.0	0	0	18.0	77.5	2.0	0	0.2	0	0.3
26	..	..	23.3	8.0	0	0	21.0	68.0	2.1	0	0.1	0	0.3
27	28	..	22.5	2.4	0.3	0	12.4	79.2	3.4	0	0.1	0	2.2
28	..	..	12.8	3.8	0	0	14.0	78.0	2.8	0.1	0.2	0.1	1.0
29	..	..	17.6	2.3	0.1	0	12.0	77.9	2.6	0	0	0.1	5.1
30	..	..	12.0	3.0	0	0	15.0	77.0	3.4	0	0.1	0	1.5
31	20	1.7	14.2	9.6	0	0	40.2	46.8	2.6	0.1	0.2	0.1	0.4
Feb. 1	..	..	13.2	9.0	0	0	16.0	72.0	3.2	0.1	0.1	0	1.6
2	..	..	8.0	7.4	0.2	0	16.2	72.0	1.4	0	0	0.2	2.6
3	..	..	8.4	8.8	0.6	0	22.6	65.0	0.6	0	0.2	0.8	1.4
4	..	1.0	14.8	8.2	0	0	20.2	63.0	4.6	0	0.4	0.4	0
5	15	0.9	11.6	6.0	0	0	18.0	70.0	4.6	0.2	0.4	0	0.8
6	22	1.6	8.8	6.0	0	0	17.0	74.0	2.8	0.1	0	0	0.1
7	25	1.7	6.0	7.2	0.2	0	25.6	63.2	1.4	0	0.4	0	1.8
8	15	1.0	9.0	6.0	0	0	24.0	64.0	8.0	0.1	0.3	0.1	2.5
9	20	1.4	10.7	7.0	0	0	19.0	66.0	7.4	0	0.1	0	0.5
10	22	1.7	10.9	6.5	0	0	16.5	68.5	8.5	0.1	0.1	0	0.3
11*													
12	30	2.2	7.6	5.8	0	0	21.8	67.6	1.6	0	0.2	0.2	2.8
13	35	2.5	9.2	4.4	0.6	0	24.4	67.6	2.2	0	0	0	0.8
14	..	..	8.3	10.0	0.4	0	30.6	54.6	2.2	0.2	0.4	0.6	0.8
15	30	1.7	15.4	7.0	0	0	20.0	67.0	2.0	0	0.2	0.2	1.6
16	30	1.4	9.2	8.0	0	0	16.0	71.4	3.6	0	0.1	0.1	0.8
17	30	1.6	9.8	8.2	0.2	0	35.6	53.0	2.0	0.2	0.2	0.4	0.2
18†													
19	32	1.7	13.8	7.2	0	0	24.0	65.4	2.5	0.3	0	0	0.6
20	30	1.6	10.2	4.0	0	0	20.0	72.0	2.5	0.1	0.2	0.2	1.0
21‡													
22	35	1.8	14.0	2.0	0	0	21.0	71.0	4.3	0	0.2	0	1.5
23	35	2.0	12.4	0.5	0	0	15.5	68.2	14.0	0.2	0.4	0	1.2
24	35	1.9	3.5	1.0	0	0	15.0	68.0	15.4	0.2	0.2	0	0.2
25	30	1.2	17.0	2.0	0	0	14.0	73.4	8.4	0	0.2	0.1	1.9
26	30	1.3	35.0	4.0	0	0	23.2	63.2	7.8	0	0.4	0	1.4
27	25	1.2	50.4	0.5	0	0	12.5	78.6	6.4	0.2	0.6	0	1.2
28	28	1.6	50.8	0.5	0	0	5.5	83.4	8.6	0.2	0.4	0.1	1.3
Mar. 1	25	1.4	50.0	0.5	0	0	4.6	89.0	3.8	0	0.2	0.1	1.8
2	30	1.8	53.0	4.8	0	0	11.2	82.0	2.0	0	0.4	0	0.6
3	30	2.0	22.0	4.2	0.6	0	16.4	74.0	3.0	0	0.2	0.2	1.4
4	28	1.6	21.2	5.2	1.0	0	14.4	64.0	11.8	0.4	1.0	0.2	2.0
5	25	1.3	64.0	5.2	1.0	0	17.2	59.6	15.0	0	0.8	0.2	1.0
6	20	1.2	56.0	7.0	0	0	14.0	58.0	16.4	1.0	0.2	0.1	3.3
7	20	1.1	41.2	6.0	0.6	0.2	16.4	66.4	9.2	0.2	0.4	0.2	1.0
8	25	1.7	60.8	6.0	0.8	0	12.8	59.8	18.6	1.0	0.2	0.4	2.2
9	20	1.5	124.0	4.2	0	0	5.0	69.2	16.8	1.6	0.4	0	2.8
10	20	1.2	152.0	2.8	0.2	0	11.2	64.0	18.0	0.4	1.0	0.2	2.2
11	25	1.6	128.0	4.8	0.4	0	9.6	65.0	17.4	0.8	0.6	0.4	1.0
12	25	1.6	160.0	2.2	0	0	6.0	64.0	24.4	1.4	1.2	0	0.8
13	..	..	168.0	2.5	0.1	0	3.9	59.4	28.9	0.5	0.3	0	4.4

* No count on this day. Transfusion, 350 cc.
† No count on this day. Transfusion, 300 cc.
‡ No count on this day.

uncommon in vitally stained preparations. The cells classified as immature monocytes corresponded in size, structure and staining reactions both in fixed and vitally stained preparations to the "hemohistiocytes" of Ferrata and the "histiocytes" described in Dameshek's cases. Included in the immature classification were very large cells with irregular, indistinct outlines, pale gray-blue cytoplasm and very large round or oval nuclei with extremely coarse reticulation. These could not be identified in vitally stained preparations and in smears they tended to occur in groups; for these reasons they were considered to be slightly damaged immature monocytes.

The myeloblasts and myelocytes which were constantly present in very small numbers were typical and bore no resemblance to the monocytic cells nor could transition forms between the two classes be seen. The plasma cells were very large, deeply basophilic, oval or irregular in contour, with large, round, eccentric, coarsely reticulated nuclei. The dark blue spongy cytoplasm not infrequently contained coarse angular azure granules.

The bone marrow was gray and dry. Smears showed immense numbers of cells identical with those predominating in the blood. Only occasionally could a myelocyte or polymorphonuclear cell be seen. Sections showed that the normal marrow structure was obliterated by masses of large mononuclear cells which seemed to have squeezed out all other types. The fragments of spleen secured were too small to give a satisfactory histologic picture. Masses of monocytes were present, but their relation to the splenic architecture could not be determined. Smears from the splenic pulp showed nothing but monocytes and erythrocytes; these smears were, in fact, almost indistinguishable from the marrow smears. Sections of the skin showed massive infiltration of the corium with large mononuclear cells; these had accumulated particularly around the sweat and sebaceous glands and in the perivascular connective tissue.

Discussion. The literature on monocytic leukemia has been reviewed recently by Dameshek,[12] who collected all cases on record up to the time of his publication. His critique of case reports appears to be accurate, except that he includes 3 cases recorded by Rosenthal[5] whereas only 1 of these is given in sufficient detail to make the diagnosis unquestionable. The clinical manifestations of monocytic leukemia are not essentially different from those of other acute leukemias; a septic type of fever, stomatitis of some degree, purpura and marked anemia have been quite constant. Splenomegaly is not usual, though it was marked in the cases of Reschad and Schilling-Torgau,[1] Merklen and Wolf,[8] Hannema[10] and Swirtschewskaja.[15] In all other instances the spleen was only slightly enlarged or was not felt. Slight to moderate enlargement of the liver has been noted in every case. Adenopathy is quite variable; when present, it has been localized in the cervical region; it does not seem to form a part of the picture. The number of leukocytes has varied widely, from 1,900[11] to 416,000.[15] Sudden marked changes in the count seems more frequent than in other types of acute leukemia and an *hiatus leukemicus* has been noted frequently. The proportion of monocytes has varied from 44 per cent[3] to 99 per cent[8] with an average of approximately 80 per cent.

Necropsies, more or less complete, have been done in 13 cases. In all there has been widespread infiltration of the tissues with monocytic cells. The lymph glands, liver, spleen and bone marrow show the most marked disturbance. The normal histology of the lymph glands and spleen is destroyed, there is proliferation of the reticulum cells and of the endothelium of the sinuses of the spleen with some evidence of actual "desquamation" of new-formed monocytes into the blood stream. In the liver the reticuloendothelial tissue is hyperplastic and the liver capillaries are crowded with monocytic cells. The bone marrow shows what may be called "monocytoid metaplasia"[12] the normal structure being obliterated by intense monocytic infiltration. The skin shows marked infiltration of the deeper layers, particularly around the glandular structures. The perivascular connective tissue of many organs shows extreme monocytic infiltration.

The diagnosis rests on the recognition of the type cell as the monocyte, either mature or immature. The adult monocyte can usually be identified without difficulty in well-stained preparations by its morphology and staining reactions. The immature monocytes ("monoblasts" of Merklen and Wolf,[8] "hemohistioblasts" (?) of Ferrata and Reitano,[17] "histiocytes" of Dameshek[12]) offer more difficulty. The large size, abundant gray-blue cytoplasm and large finely reticulated nucleus of these cells make them striking objects in fixed smears. Supravital staining is characteristic and is the most important diagnostic procedure, differentiating them satisfactorily from cells of the myeloblastic series.

Monocytic leukemia must be differentiated from other acute leukoses, in particular from certain cases of acute myeloblastic leukemia in which there is a predominance of myeloblasts with lobed nuclei. Infectious mononucleosis may at first arouse suspicion of this condition but the absence of immature forms and the benign progress of the disease should speedily remove doubt, the same being true of the mononucleosis following administration of arsphenamin. Agranulocytosis has doubtless been confused with monocytic leukemia,[7] but in the latter condition there is never a complete absence of granular leukocytes nor do immature monocytes occur in agranulocytosis.

The acceptance of monocytic leukemia as a clinical and pathologic entity involves recognition of the validity of the newer conception of the derivation of the circulating monocytes directly from reticuloendothelial tissue. The investigations of Kiyono,[19] Maximow[20] and Sabin[21,22] have gone far toward the proof of this theory which has been advanced by numerous observers and which offers a logical classification of leukemic monocytosis as a system disease. The occurrence of myeloblasts and myelocytes, particularly in the later stages of the disease, has led many authors to classify these cases as

unusual types of myeloses. Naegeli[23] is a vigorous exponent of this view. It seems more reasonable to assume that the intense monocytic proliferation in the marrow forces a certain number of immature marrow cells into the circulation, and this assumption seems strengthened by the constant occurrence of a marked actual as well as relative granulocytopenia.

Conclusions. A case is recorded in which the diagnosis of acute monocytic leukemia was made. Although multiple infections were present, negative cultural studies and the course of the disease seemed to eliminate pyogenic infection as a cause of the blood picture.

The type cell in both mature and immature stages was adequately identified with peroxidase and supravital as well as the conventional stains. It was differentiated from cells of the myeloid and lymphatic series as belonging to the monocyte series.

A direct derivation of the monocyte from the reticuloendothelium offers a logical explanation of the occurrence of this type of leukemia.

NOTE.—Since the preparation of this paper additional instances have been reported by Cooke, W. E., Lancet, 1931, **2**, 129; Lawrence, P. S., Posey, A. I., and Young, M. W., Folia hematol., 1931, **44**, 332; Rirks, W. W., Jr., and Cunningham, R. S., South. Med. J., 1931, **24**, 1089.

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THE HEMATOPOIETIC RESPONSE IN PERNICIOUS ANEMIA FOLLOWING THE INTRAMUSCULAR INJECTION OF GASTRIC JUICE.*

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The treatment of pernicious anemia has undergone rapid advance in recent years. The introduction of the liver diet by Minot and Murphy[1] was the first great step forward, and was soon followed by liver extract.[2] Working on an original theory, Sharp[3] introduced hogs' stomach (ventriculin), which Sturgis and Isaacs[4] proved to be efficacious therapeutically. Quite independently, Conner[5] and Wilkinson[6] also employed hog's stomach in the treatment of the disease. Later, Gänsslen[7] and Castle[8, 9] prepared liver extracts for parenteral use.

Achylia gastrica has long been considered to be an important diagnostic criterion of pernicious anemia. The illuminating studies of Castle[10–14], however, have thrown new light on the importance of this factor. He and his coworkers have shown that there is an unknown substance present in normal gastric juice which is lacking in the secretion of the stomach in pernicious anemia. They have shown that the feeding of beef which has been digested by normal gastric juice causes a reticulocyte response in pernicious anemia, whereas beef digested with gastric juice from a patient with pernicious anemia has no such effect. Further, during a remission, the gastric juice of the patient with pernicious anemia becomes active, like normal gastric juice. It was further demonstrated that feeding of 300 cc. of normal gastric juice without beef daily for 10 days was ineffective.

The unknown substance is destroyed, they have shown, by boiling for 5 minutes, by heating to 70 to 80° C. for a half hour or by exposure to a temperature of 40° C. for 3 days.

As a result of these brilliant researches, it seemed to us quite possible that the normal stomach secretes a substance (probably

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the same substance which Castle has shown to be present) which, while without effect on the reticulocytes when administered orally, might cause a response if it could be administered parenterally. In order to test this theory, we[15,16] proceeded as follows: Normal gastric juice was collected from patients free from anemia following lavage and the administration of histamin. The juice was rendered neutral to litmus, and after cultures had proved sterility, it was injected intramuscularly, first in rabbits and later in man, without undue local or general reaction. Autopsy revealed no lesions in the muscles of rabbits at the site of injection. A patient dying of acute leukemia into whose gluteal muscle gastric juice was injected came to autopsy. Microscopic examination of the muscle showed no noteworthy change. Intravenous injections were tried, but were abandoned temporarily because of rather severe general reactions.

Next, neutralized sterile juice was given intramuscularly in amounts up to 20 cc. to a patient with pernicious anemia. The reticulocyte response was so slight as to be negligible, though sufficient to warrant further study. Attempts were now made to concentrate the gastric juice. This was done by allowing it to evaporate in dishes placed in the incubator at 38° C. to about 3 to 5 per cent volume. This required between 2 and 3 days. We secured a preparation with definite activity, one which gave an increase of reticulocytes to about 6 per cent in a patient who had 1 million red cells. The response was quantitatively far below that obtained with liver extract or ventriculin. But the publication of Castle's observations on the effect of heat on the unknown substance, particularly its destruction by exposure to 40° C. for 3 days, made it seem probable to us that our material had been partially inactivated in our method of concentration. On the advice of Dr. G. E. Cullen of the Department of Pediatrics, whose helpful suggestions we acknowledge gratefully, vacuum distillation of the gastric juice at a temperature not exceeding 40° C. was tried. By this method it is possible to reduce the volume to about 3 per cent in 2 to 4 hours.

Normal human gastric juice, concentrated by distillation *in vacuo*, was now given to patients with pernicious anemia. The injection of the equivalent of 450 cc. of gastric juice to a patient with 2.1 million red cells led to a reticulocytosis of 17.6 per cent in 36 hours. Twelve days after the injection, the red count and percentage of hemoglobin began to increase. Within the period of the next 12 days, the count increased by 1.5 million cells and the hemoglobin by 20 per cent. The count then remained stationary until further treatment was instituted. A second patient who received intensive intramuscular treatment with Lilly's liver extract No. 343, improved after this until the red count reached 4.1 million, where it remained for 4 weeks, despite daily intramuscular injections of 4 cc. Then, an intramuscular injection of the equivalent of 300 cc. of human gastric juice was given. Within 14 days, the red count had increased

to 5.1 million and the hemoglobin had risen from 76 per cent to 88 per cent when the patient was discharged. The reticulocytes rose from 0.5 per cent to 2.7 per cent within 9 hours after the injection.

The results obtained in these patients prove the presence in normal gastric juice of a powerful bone marrow stimulant, one which produces not only a marked and very rapid reticulocyte increase after intramuscular injection but also rapid maturation of the red cells.

With the reticulocytosis, we have also found a still earlier increase in red cells containing nuclear particles. The majority of the latter are minute, about pin-point in size. The cells containing them are usually polychromatophilic and the reaction is looked upon as analogous to the reticulocytosis.

There is also an increase in the total white count and in the percentage of neutrophil cells within a few hours after the injection, as well as an increase in the number of blood platelets. This reaction subsides within 1 to 2 days. Following the injection, the eosinophils gradually increase, reaching the peak usually on the fifth day.

In the process of concentration of human gastric juice *in vacuo*, a sediment forms. Injection of this sediment is not followed by an increase of the reticulocytes. The supernatant fluid, on the other hand, is highly active.

Boiling the supernatant fluid for 5 minutes destroys the substance which causes the reticulocytosis and the increase in nuclear particles. But it is noteworthy that injection of the boiled supernatant fluid produces a prompt neutrophilic leukocytosis. Therefore, the substance causing reticulocytosis is not that which causes the neutrophilic leukocytosis.

The unknown substance present in normal gastric juice is dialysable, passing through a collodion sac. In this connection it is of interest that the anti-anemic factor of stomach tissue is also recoverable in the dialysate.[17] This indicates that its molecular structure is relatively simple. That the increase in red cells and hemoglobin, once begun, does not continue until normal values are reached shows that it is exhaustible and, therefore, probably not an enzyme. It is soluble in acetone.

More recently, through the coöperation of Dr. E. A. Sharp, Director of the Department of Experimental Medicine of Parke, Davis and Company, we have obtained the gastric juice of swine. With this material, we have obtained an increase in the reticulocytes in pernicious anemia, the results being analogous to those obtained with human gastric juice, though less pronounced quantitatively. We have noted the same increase in nuclear particles, the neutrophilic leukocytosis and the increase in blood platelets, though the response has been less prompt. With certain modifications in the method of preparation, it has been possible to obtain a product from swine which produces no leukocytosis, a slight local reaction with

practically no fever and a reticulocyte response which begins on the third day, after a single injection equivalent to 500 cc. of original volume. We are at present trying to obtain greater potency through refinements in the method of preparation.

Sixty-two intramuscular injections of gastric juice, varying in amounts from 5 cc. to 25 cc., have been given up to the present time (April 27). These have been given deep into the muscles of the buttocks or thighs, either preceded or accompanied by sufficient procain to make a 1 per cent solution. Pain at the site of injection is the most prominent symptom, being present in nearly every case. It is often complained of during the injection but usually develops about 2 hours later, lasting from 6 hours to 4 days, varying a great deal in severity. Occasionally there is some induration of the tissues, but usually the only local reaction is marked tenderness over the area. The temperature has been elevated after about two-thirds of the injections, ranging from 99° to 102° F., appearing from 6 to 12 hours later. Temperatures of 103° and 104° F. have been reached 5 times. Slight chills have occurred twice after intravenous injections and once following an intramuscular injection. Nausea and vomiting occurred after 2 injections in 1 patient and once in each of 2 other patients. Circulatory failure occurred in 1 patient and was relieved by adrenalin. This was probably due to accidental injection into a vein as this patient has received numerous injections since that time without circulatory disturbance. Rather marked flushing of the face and hands was present after 15 of the injections, coming on within 5 minutes after the injection and lasting for 1 to 2 hours. Severe frontal headaches lasting from 2 to 6 hours have occurred 5 times. There has been only slight elevation of the pulse rate following these injections. Since we have been using the acetone extracted swine juice there has been practically no febrile reaction, and the pain has been much less severe and of shorter duration. Flushing of the skin and headache have been noticed only since using the acetone extract.

The anti-anemic substance of gastric juice is thermolabile, dialysable and exhaustible, and is probably a hormone, for which we have proposed the name *addisin*, after Thomas Addison, who first described pernicious anemia. The evidence at hand indicates that this is the physiologic stimulant of the bone marrow which maintains the blood cells and hemoglobin at a normal level.

Conclusion. It seems highly probable that the temporary lack of addisin in the gastric juice is the cause of pernicious anemia. Its administration intramuscularly has proved to be efficacious therapeutically in this disease, and it may be found to be of value in other blood dyscrasias. What effect it may have on the cord changes in pernicious anemia has not been determined.

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PERICARDIAL EFFUSION: A CLINICAL STUDY.

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The diagnosis of pericardial effusion proven by autopsy has never reached a high degree of accuracy and the low percentage of correct diagnosis is at first thought appalling. When one considers, however, that the normal heart volume displacement is about 750 cc., that it requires a good deal of effusion to add appreciably to this volume, that in a great number of cases in which one finds pericardial effusion one also finds an enlarged heart, and that the effusion is very apt to be a terminal event in a very sick patient, then the diagnostic error is not so glaring.

Historical Review. It is known that the ancients, including Galen, were aware of changes in the pericardium of animals and man. In more modern times Riolan (1646) and Senac (1749) among others described pericarditis with effusion in man. Rondelet and Riverius were able to recognize some of the symptoms of pericardial disease, and their descriptions were added to by Morgagni and others. By the method of immediate percussion Auenbrugger

was able to determine that in some cases of pericardial effusion there was an increase in cardiac dullness, but this observation was put on a much firmer basis by his translator Corvisart, who worked on the subject independently. Laennec is often credited with the discovery of the pericardial friction rub but it seems most certain that the honors should go to his assistants Collin and Devilliers who demonstrated that the friction sound of "creaking leather" was caused by pericarditis.

Pitcairn in 1788 showed the relationship of rheumatism and pericarditis. Since then there have been many etiologic factors discovered and described in the literature, but today as then the rheumatic infection accounts for a large number of cases of pericarditis, perhaps more than any other single etiologic factor.

Pericardial paracentesis was first suggested in 1646 by Riolan; however, this was not actually performed until the year 1819 at which time it was done by Romero of Barcelona. Jowett of Nottingham was the first to use the trocar in doing a pericardial paracentesis. This method was brought into more general repute by Schuh of Vienna in 1839, by Trousseau of France in 1854, and by Allbutt in England in 1866. Thayer and also Shattuck removed by aspiration as much as 1250 cc. a good many years ago. The largest amount of effusion obtained at autopsy was reported by Verney in a case from which he collected 4000 cc. It is interesting to note that in this case pericardial taps had been done on two occasions several days before death, 400 cc. being obtained at one time and 500 cc. at the other. Gibson mentioned a case recorded by Corvisart in which he states that he found 4000 cc. of pericardial fluid.

Experimental work on the pathologic physiology of pericardial effusion was first done by François-Franck in 1877. He demonstrated that, due to its pressure, fluid injected into the pericardial cavity hinders the entrance of blood into the auricles and causes stasis of the blood in the venæ cavæ and a fall in blood pressure. Shortly after this, Lagrolet and Cohnheim experimented with injections of fluid into the pericardium. Starling repeated these experiments and came to the same conclusion as did François-Franck. Many other experiments have been done to attempt to explain the mechanism of pulsus paradoxus, the position assumed by the heart during pericardial effusion, the sites of collection of the fluid within the pericardium, and the physical signs produced by the fluid.

Gauchat and Katz deduce from their experiments with pericardial effusion that the paradoxical pulse is best explained as follows: "With the pericardium distended with fluid, not only is the flow of blood into the heart impeded but the inflow also varies during inspiration and expiration, owing to the fact that the respiratory variations of intrathoracic pressure do not affect the intrapericardial and intracardiac pressures as much as those in the entering veins. This causes a smaller difference of pressure between the veins and

heart during inspiration and allows less filling of each ventricle. Consequently a paradoxical pulse probably appears in both the pulmonary and systemic circuits but obviously the arterial pulsus paradoxus is due to the impaired flow into the left ventricle." Lewis has demonstrated that pulsus paradoxus can easily be produced in a normal person by forced respiration. The mechanism of this is not clear for there is still a decrease of intrathoracic pressure with inspiration and a tendency to an increase of blood flow to the heart. The decreased pressure in the arm artery here is probably not due to any decreased output from the heart, but rather to a compression of the subclavian arteries by the elevation of the chest as the result of increased respiratory effort. Where there is a massive pericardial effusion a marked pulsus paradoxus may occur. The mechanism is probably not wholly like that associated with thoracic breathing without pericarditis, although the thoracic inspiration may still be one factor; the new element of obstruction to the inflow of blood into the heart acts to decrease considerably the size of the pulse in both inspiration and expiration and thus to accentuate the pulsus paradoxus, so that in some cases the pulse may actually disappear during inspiration. However, we have not yet a completely satisfactory explanation for the important sign of the pulsus paradoxus in the presence of considerable pericardial effusion.*

Williamson by injecting a material which hardened after injection concluded as follows from his experiments: (1) In pericardial effusion fluid accumulates first along the lower margin of the heart and about the apex, particularly on the diaphragmatic surface of the heart, and in small effusions this is the only place of regular accumulation. (2) The second place of accumulation is over the great vessels. (3) In at least 14 of 33 cases of pericardial effusion the anterior surface of the heart remained in part uncovered by fluid so that a friction rub could easily exist. This last point is of interest and may explain such cases as reported by Cejka in which a friction rub persisted even when the sac contained 1000 cc. of fluid, and by Porter in which he heard a definite pericardial friction rub just before the aspiration of 1350 cc. of fluid, while a Roentgen ray taken immediately after aspiration showed that only a portion of the fluid was removed.

Cabot stated that with clinical methods not less than 150 cc. of fluid can be recognized. Aporti and Figaroli found no changes in cardiac dullness until about 400 cc. had been injected. Morris and Bader found that at least 500 cc. must be present before it can be detected with the patient in the recumbent position.

Cabot in his book *Facts on the Heart* has reported the results

* Inspiration may act to reduce the inflow of blood into the heart in the presence of extensive pericardial effusion by allowing the pericardial fluid more completely to compress the roots of both venæ cavæ which are elongated and thus more easily collapsed upon descent of the diaphragm.

of his studies of the autopsies at the Massachusetts General Hospital from 1897 to 1919. His findings are briefly as follows: (1) 186 cases of acute pericarditis with or without effusion were found; 141 males, 45 females. (2) Rheumatism in the ordinary sense is only a minor factor in the production of pericarditis. There was a clear rheumatic history in only 12 per cent. (3) Pericarditis is primarily a terminal affair. (4) A friction rub was heard in only 21 per cent of the cases. (5) Sixty-eight of the 186 cases showed 100 cc. or more of exudate: 100 cc. in 7 cases; 150 cc. in 5; 200 cc. in 4; 250 cc. in 1; 200 to 300 cc. in 2; 300 cc. in 4; 300 to 400 cc. in 1; 400 cc. in 1; 500 cc. in 1; 700 cc. in 1; unmeasured in 41. (6) All of these 68 cases, Cabot believes, might have been recognized in life; however, only 7 cases (10 per cent) were so recognized. The Roentgen ray in this early series was rarely used. (7) There was failure to recognize clinically pericarditis either with or without effusion in 77 per cent of the cases. (8) With more frequent use of radioscopy this record should be greatly improved, was Cabot's conclusion.

Present Study. With Cabot's studies in mind, we have conducted the present investigation in order to determine the present status of the diagnosis of pericardial effusion. The material selected for study is composed of three groups: (1) The cases of the general services of the Massachusetts General Hospital in which pericardial fluid of 100 cc. or over was found postmortem, (2) the cases of the Eye and Ear Infirmary of similar nature, and (3) a group of cases in which fluid was obtained by antemortem pericardial paracentesis, thus warranting a diagnosis of pericardial effusion. The material in the above mentioned groups was collected from the records over a ten-year period, from January 1, 1921, to December 31, 1930.

Group I. Postmortem Group of Cases of Pericardial Effusion. There were 95,542 cases admitted and 1729 autopsies performed on the general services of the Massachusetts General Hospital in the 10-year period, 1921 to 1930, inclusive. Of the 1729 autopsies, 126 (7.2 per cent) showed a pericardial effusion of 100 cc. or more. There were 75 males and 51 females; the average age was 43 years and the age incidence by decades was as follows: first 4, second 11, third 21, fourth 25, fifth 15, sixth 22, seventh 22, eighth 5, and ninth 1. The youngest patient was 5 months old and had a purulent pericarditis due to the Bacillus influenzæ and the pneumococcus; the oldest case of 84 years had a rupture of a dissecting aortic aneurysm into the pericardial sac.

A. Cases with 100 to 250 cc. of Pericardial Fluid. There were 94 cases, 60 males, 34 females; the average age was 40 years.

1. *Cases without Pericarditis.* There were 72 cases, male 44, female 28; the average age was 42 years.

Etiology. This group presents some very interesting points in etiology.

Twenty-six cases may be classed under the general heading of

chronic passive congestion mostly due to cardiac failure. This subgroup may be further divided as follows: 5 cases associated with definite nephritis without hypertension, 5 cases associated with hypertension but without nephritis, 8 cases with rheumatic heart disease, 2 cases with a question of hypertensive heart disease (in other words, although no definite hypertension was found, it was thought after considering the clinical history that a previous hypertension had existed), 2 cases associated with coronary occlusion, 1 case associated with an extensive chronic pleurisy in which the mechanism of production of the chronic passive congestion was unknown but was probably due to obstruction, and 1 case each associated with subacute bacterial endocarditis, questionable rheumatic heart disease, and arteriosclerosis.

We have classified 24 other cases under the head of infections of various types with a question as to the mechanism of production of the pericardial effusions. In none of these was there a demonstrable pericarditis at necropsy. The subdivision of this group follows: 13 cases associated with lobar pneumonia or bronchopneumonia, 4 cases with empyema or pulmonary abscess, 3 cases with streptococcus infection, 1 case of Bacillus coli infection and 3 cases of infection in which the infecting organism was not found.

Three other cases were diagnosed clinically and at autopsy as chronic passive congestion but no pleural effusions were found in them. This brings up the question as to whether or not fluid may collect in the pericardial sac and not also in the pleural cavities in cases of chronic passive congestion. These 3 cases were associated with the following: (1) chronic rheumatic heart with subacute bacterial endocarditis, (2) pernicious anemia, (3) nephritis and hypertension.

There are 2 cases associated with nutritional edema and 1 case with the nephritic edema of Fahr.

We found 8 other cases associated with malignancy not involving the pericardium.

An additional case presented chronic rheumatic heart disease with acute pulmonary edema; the pericardial as well as pleural fluid was bloody and we thought of the possibility of rupture of engorged vessels as a cause of this effusion. The remaining 7 cases of this group were associated with conditions in which the mechanism of the collection of the fluid was entirely unknown and were composed as follows: 2 cases of miliary tuberculosis (without pericardial involvement); 1 case of lues; 1 case of lues and tuberculosis combined; 1 case of myxedema; 1 case of unknown cause with a questionable diagnosis of lues and Ayerza's disease; and 1 case of cirrhosis of the liver.

The type of pericardial fluid in these 72 cases was as follows: clear, 54; "amber," 14; turbid, 1; serosanguineous, 1; bloody, 2.

Pleural effusions of 500 cc. or over were found in 32 of these 72 cases, and of less amount in 15 others; the fluid was clear in 27 cases, turbid in 11, bloody in 6, and purulent in 3.

Symptoms. Precordial pain was present in 12 cases and absent or not mentioned in 60 cases. Dyspnea was present in 38 cases and absent in 34 cases.

Signs. A definite pericardial friction rub was not mentioned in any of this group; it was questioned on 2 occasions, noted as absent in 2 cases, and not mentioned in the remainder. Murmurs were present in 33 cases.

Heart Weights. The heart weight was recorded in 67 of the 72 cases; it was less than 300 gm. in 15 cases, 300 to 500 gm. in 30 cases, and over 500 gm. in 22 cases.

Electrocardiograms. These were not very enlightening and the classifications as given necessarily overlap. We found the following in 12 of the 72 cases electrocardiographed; normal rhythm, 6 cases; partial auriculoventricular block, 4 cases; premature beats, 2 cases.

Radiographic Examination. A correct Roentgen ray diagnosis was not made in any of 26 instances examined by Roentgen ray; the diagnosis of pericardial effusion was questioned 3 times and missed in the other 23 patients.

Clinical Diagnosis. Not one of the 72 cases was diagnosed as pericardial effusion; the diagnosis was questioned in 1 case which was seen by the medical service. The medical service alone examined 34 cases, the surgical service alone examined 5 cases, the pediatric service alone 1 case and cardiac consultants examined 16 cases. The remaining 16 cases were seen by the general services together, mostly the medical service in consultation with the surgical. The conditions of the patients were as follows: acutely ill, 33; moribund, 11; chronically ill, 24; died suddenly, 4.

2. *Cases with Pericarditis.* This group was composed of 21 cases, 15 males and 6 females; the average age was 42 years.

Etiology. The pericarditis was due to several types of infection or uremia as follows: pneumococcus Type II, 1; Bacillus influenzæ and pneumococcus, 1; pneumonia without specified organism, 2; Staphylococcus aureus, 2; streptococcus, 4; purulent lung infections, 2; acute rheumatic heart disease, 4; subacute bacterial endocarditis, 1; infection associated with lues, 2; and uremia, 2.

The *character of the pericardial fluid* was found to be as follows: serofibrinous, 9 cases; turbid, 1; serosanguineous, 1; bloody, 1; and purulent, 9.

Pleural effusions of 500 cc. or over were found in 9 cases, of less amount in 7 cases, and no pleural effusions were noted in 5 cases. The fluid was clear in 7 cases, turbid in 2, and purulent in 7.

Symptoms. Dyspnea was present in 9 cases, and absent or not mentioned in 12 cases. Precordial pain was noted in only 2 cases.

Signs. A pericardial friction rub was heard in 3 cases. Murmurs were present in 12 cases.

Heart Weights. Hearts weighing less than 300 gm. were found in 6 cases, 300 to 500 gm. in 8, and over 500 gm. in 4; the weights were not recorded in the remaining 3 cases.

Electrocardiograms. Electrocardiograms were taken in only 2 cases, 1 of which showed normal rhythm and the other auricular fibrillation. Neither record showed low voltage.

Radiographic Examination. A Roentgen ray diagnosis of pericardial effusion was correctly made in 1 case; in the other 7 cases examined by Roentgen ray a pericardial effusion was not diagnosed once.

Clinical Diagnosis. Of the 21 cases in this group, 4 were correctly diagnosed clinically. The medical service alone examined 7 cases and made a correct diagnosis once; the surgical service alone examined 5 cases and also made one correct diagnosis; the pediatric service examined 1 case without correct diagnosis; the medical and surgical services combined saw 3 cases and failed to make the diagnosis in any of them; cardiac consultants saw 5 cases and diagnosed 2 of these correctly. Twelve of the 21 patients were acutely ill, 1 moribund, 1 died suddenly, and 7 were chronically ill.

3. *With New Growth Involving the Pericardium.* In this group there was 1 case, a male aged 36 years. His pericardial fluid was of amber color. Pleural fluid was present, over 500 cc. in amount and bloody. Pain and dyspnea were absent. A friction rub was not mentioned, but there was an apical systolic murmur. The heart weighed less than 300 gm. An electrocardiogram was not obtained. The Roentgen ray diagnosis of pericardial effusion was not made nor was the correct clinical diagnosis made. The patient was chronically ill.

Summary of Class A. Cases with 100 to 250 cc. of Pericardial Fluid. There were 94 cases in this group, 60 males and 34 females, the average age being 40 years. Twenty-one cases showed a pericarditis, 72 cases did not have a demonstrable pericarditis, and there was 1 case of new growth involving the pericardium by metastasis. In the group with pericarditis the etiologic factor was infection of some type in all except 2 cases which were associated with uremia; in the group without pericarditis chronic passive congestion was the most important factor while infections of various types but not involving the pericardium in a demonstrable way account for the next largest group; the remainder were associated with miscellaneous diseases such as malignancy, tuberculosis, nutritional edema, lues, and acute pulmonary edema. The pericardial as well as pleural effusions varied according to the nature of the etiologic agent. Dyspnea was present in 47 cases; pain was noted in 14 cases. Friction rubs were heard in only 3 cases. Murmurs were heard in 46 cases. The orthopneic position was assumed by

25 patients. Cervical veins were noted as distended in only 2 cases and heart sounds were noted as distant in 21 cases. A pulsus paradoxus was not recorded in any case. The electrocardiograms were not significant. A correct Roentgen ray diagnosis was made in 1 case, and questioned in 3 of the 35 cases examined. A correct clinical diagnosis was made in 4 and questioned in 1 other of the total of 94 cases.

B. Cases with 250 to 500 cc. of Pericardial Effusion. 1. *Cases without Pericarditis.* Twenty belong in this group; 13 males and 7 females.

Etiology. Here again we found that the largest etiologic factor was chronic passive congestion due to heart failure. There were 11 such cases, associated as follows: with hypertension in 1 case, questionable hypertension in 3, nephritis and hypertension in 1, calcareous valvular heart disease in 1, chronic rheumatic heart disease in 4, and bronchopneumonia in 1. There were 4 cases of myocardial infarction and 1 case each of the following: ruptured aortic aneurysm, myelogenous leukemia, tuberculosis associated with Hodgkin's disease, and subacute bacterial endocarditis due to infection with the Streptococcus viridans.

The pericardial fluid was clear in 16 of the 20 cases, "amber" in 2, and bloody in 2.

Pleural effusions were noted in 13 cases, being over 500 cc. in amount in 9 of these. The pleural fluid was clear or turbid in 8 of these 13 cases, bloody in 4, and purulent in 1.

Symptoms. Six cases showed precordial pain. Dyspnea was present in 16 cases and absent in 4.

Signs. A pericardial friction rub was questioned in 1 case and not mentioned and apparently absent in the remaining 19. Murmurs were present in 13 cases and noted as absent in 7 cases.

Heart Weights. Of the weights recorded in 18 cases we found the following: less than 300 gm., 2 cases; 300 to 500 gm, 6 cases; over 500 gm., 10 cases.

Electrocardiograms. Electrocardiograms were taken in 3 cases which showed, respectively, the following points of interest: (1) inverted T_2 and left axis deviation; (2) partial auriculoventricular block with P–R interval of 0.22 second and also intraventricular block; (3) left axis deviation and auricular and ventricular premature beats. Low voltage was not present in these 3 cases.

Radiographic Examination. A correct Roentgen ray diagnosis was not made, but was questioned once, in the 6 cases examined.

Clinical Diagnosis. In none of this group was a clinical diagnosis of pericardial effusion made, but in 1 case examined by the medical service this diagnosis was questioned. The medical service alone examined 14 cases, the surgical alone and the medical and surgical combined saw 1 case each, and the cardiac consultants examined 4 cases. The conditions of the patients were as follows:

acutely ill, 5; chronically ill, 5; intermediate, 10; 2 cases were moribund and 3 cases died suddenly.

2. *Cases with Pericarditis.* Only 2 cases occurred in this group; both were females.

Etiology. Nephritis was present in 1 case; an infection by undetermined organism existed in both.

The *pericardial fluid* was serofibrinous in both cases.

One had over 500 cc. of *pleural effusion* and the other less; the pleural fluid was purulent in both.

Symptoms. Both pain and dyspnea were present in 1 case but were absent in the other.

Signs. A pericardial friction rub was present in both cases. A murmur was present in 1 and absent in the other.

The *heart weight* was recorded in 1 case as between 300 and 500 gm.

Radiographic Examination. Only 1 case was examined and the correct diagnosis was questioned in this instance.

Electrocardiogram. The 1 case examined electrocardiographically showed ventricular premature beats and a diphasic *T* wave in Lead 2; the voltage was not low.

Clinical Diagnosis. The medical service examined these 2 cases; 1 was moribund and 1 chronically ill; the clinical diagnosis of pericardial effusion was not made in either case.

3. *New Growth Involving the Pericardium.* There were 2 cases in this group of malignancies of the pericardium; 1 male, and 1 female.

The *pericardial fluid* was clear in 1 case and bloody in the other. One case contained less than 500 cc. of purulent pleural fluid.

Symptoms. Dyspnea was present and pain was absent in both cases.

Signs. A pericardial friction rub was not mentioned in either case; 1 case had a murmur and the other did not.

The *heart weight* was recorded in 1 case as between 300 and 500 gm.

Electrocardiograms were not done.

A correct *Roentgen ray diagnosis* was not made in either case.

Clinical Diagnosis. One case was examined by the cardiac consultants and 1 by the medical and surgical service combined; a clinical diagnosis of pericardial effusion was not made in either case. One patient was acutely ill, the other moribund.

Summary of Class B. Cases with 250 to 500 cc. of Pericardial Effusion. This group contained 24 cases altogether: 15 males and 9 females. Twenty cases showed no pericarditis, while there were 2 cases each of pericarditis and of malignancy involving the pericardium. In the group without pericarditis chronic passive congestion was found to be the main etiologic factor, cardiac infarction was next in importance, and the remaining cases presented a variety of diseases. In the 2 cases with pericarditis nephritis was present in 1, and in both cases an undetermined organism was responsible

for infection elsewhere in the body. The pericardial fluid varied according to the type of disease. Pain was present in 7 cases and dyspnea in 18 cases. A pericardial friction rub was heard twice and questioned once. Heart sounds were noted as distant in 6 cases. A pulsus paradoxus was not recorded in any case. The cervical veins were distended in 3 cases but this finding may have been due to the congestive heart failure. Ten patients out of the 24 elected the orthopneic position. The electrocardiograms were not significant. Of 9 patients examined by Roentgen ray 8 were not diagnosed as pericardial effusion; the diagnosis was questioned once. Clinically the diagnosis of pericardial effusion was not definitely made in any case; it was questioned on only one occasion.

C. Cases with Over 500 cc. of Pericardial Effusion. 1. *Cases without Pericarditis.* There were 5 cases with over 500 cc. in this group: 2 males and 3 females.

Etiology. The etiological factor was as follows: chronic passive congestion in 3 cases (1 case each associated with subacute bacterial endocarditis, questionable rheumatic heart disease and infection with the Streptococcus hemolyticus, and myxedema), tuberculosis in 1 case associated with doubtful chronic passive congestion, and, finally, unknown mechanism in 1 case of heart disease.

The *pericardial fluid* was clear in 3 cases and bloody in 2.

Four cases had *pleural effusions* of over 500 cc.; in 3 of these the pleural fluid was clear and in 1 bloody.

Symptoms. Pain was absent in all 5 cases. Dyspnea present in 2.

Signs. A pericardial friction rub was recorded as present in 1 case and not mentioned in 4 cases. Murmurs were present in all 5 cases.

Heart Weights. The heart in 1 case weighed less than 300 gm., in 4 cases it weighed over 500 gm.

Electrocardiograms were done on 3 cases, 2 of which showed low voltage; the other 1 showed diphasic *T* waves in Leads 1 and 2.

Radiographic Examination. Of 4 cases examined by Roentgen ray the diagnosis of pericardial effusion was questioned once and not noted in the other 3.

Clinical Diagnosis. The medical service examined 3 cases but did not diagnose pericardial effusion. The cardiac consultants examined 2 cases and made the correct diagnosis once.

2. *Cases with Pericarditis.* Only 1 case occurred in this group. It was an instance of polyserositis in a woman aged 21 years.

The *pericardial fluid* was serosanguineous.

There was a *pleural effusion* of over 500 cc. which was turbid.

Symptoms. Pain and dyspnea were both present in this patient.

Signs. A pericardial friction rub was present in addition to a systolic apical heart murmur.

The *electrocardiogram* showed low *T* waves in all leads and small complexes.

In a *radiographic examination* the diagnosis of pericardial effusion was questioned.

A cardiac consultant saw this patient in consultation with the medical service; the correct clinical diagnosis was made. The patient was chronically ill.

3. *Malignancy Involving the Pericardium.* There were 2 males in this group of malignancy secondarily involving the pericardium.

Bloody pericardial effusion was found in both.

There was a clear *pleural effusion* in both cases, 1 of more than 500 cc.

Symptoms. Pain and dyspnea were present in these 2 cases.

Signs. A pericardial friction rub was noted as absent in 1 case and not mentioned in the other. Murmurs were not heard.

In the 1 case examined by *Roentgen ray* a pericardial effusion was not diagnosed.

Both of these cases were seen by the medical and surgical services together; a diagnosis of pericardial effusion was not made. The patients were chronically ill.

Summary of Class C. Cases with 500 cc. or More of Pericardial Effusion. We found in this group 8 cases, 4 males and 4 females. In only 1 case did pericarditis occur; 2 cases had malignant disease involving the pericardium. Five cases had no pericarditis and of these 5 cases 3 had chronic passive congestion; in the other 2 the mechanism of the production of the pericardial fluid was not evident. The pericarditis was associated with polyserositis in 1 case. The pericardial fluid was serosanguineous or bloody in 4 cases and clear in 4. Pain was present in 3 cases and dyspnea in 2. The orthopneic position was noted in 2 patients but there was no statement of distention of the cervical veins. Heart sounds were recorded as distant in 2 cases. The presence or absence of the pulsus paradoxus was not noted. The electrocardiograms in this group showed a constant tendency to small complexes. Of the 5 cases examined by Roentgen ray the diagnosis of pericardial effusion was not made positively in any; it was questioned in 1 case. The correct clinical diagnosis was made in 2 cases, 1 with and 1 without pericarditis.

D. Six Cases of the Postmortem Series of Pericardial Effusion Correctly Diagnosed Clinically. 1. *Cases with 100 to 250 cc. of Pericardial Fluid.* Four cases occurred in this group, 3 males and 1 female; the average age was 37 years.

Etiology. All 4 cases had pericarditis, due in 2 to acute rheumatism and in the remaining 2 to other acute infection, Staphylococcus aureus in 1 and an undetermined organism in the other.

The *character of the pericardial fluid* was as follows: serofibrinous in 2 cases, bloody in 1, and purulent in 1.

Two cases had *pleural effusions* of over 500 cc. and 1 had less than that amount; the pleural fluid was clear in 2 cases and turbid in 1 case.

Symptoms. Pain was present in 1 case; dyspnea was present in all 4 cases.

Signs. A pericardial friction rub was noted as present in 2 cases and absent in 1. Heart sounds were distant in 2 instances. The pulsus paradoxus was present in 1 case during an operation of pericardiotomy but disappeared about 12 hours later; it was not noted before the operation. The cervical veins were distended in 1 case, and 3 patients assumed the orthopneic position.

An *electrocardiogram* was done in 1 case with acute rheumatic pericarditis; it showed sinus arrhythmia and bradycardia, with poorly marked *P* waves and intraventricular block.

A correct Roentgen ray diagnosis was made in 1 out of 3 cases examined.

Pericardial paracentesis was attempted in 2 of these 4 patients. One case yielded 32 cc. of purulent fluid and, when a pericardiotomy was performed later, about 50 cc. of Staphylococcus aureus pus was removed. Several taps were tried in different locations on the other patient but only 5 cc. of blood were obtained. It is interesting to note that in this case on postmortem examination the fluid was found to be encapsulated.

2. *Cases with 250 to 500 cc. of Pericardial Fluid.* There were no cases in this group diagnosed correctly before death.

3. *Cases with Over 500 cc. of Pericardial Fluid.* There were 2 cases in this group.

One case was a woman aged 21 years with polyserositis. The pericardial fluid of 800 cc. was purulent. There was also a pleural effusion of 500 cc. in amount; this pleural fluid was turbid. Both pain and dyspnea were present in this case. A pericardial friction rub was present. The character of the heart sounds was good; systolic and diastolic murmurs were heard at the base of the heart. Neither pulsus paradoxus, nor condition of cervical veins, nor position of the patient was mentioned in the record. The electrocardiogram presented rather low *T* waves and small complexes in all leads. The Roentgen ray report stated that there was no positive evidence of fluid in the pericardium.

The other case was one without pericarditis in a man, aged 32 years. The etiologic factor was chronic passive congestion associated with subacute bacterial endocarditis. Five hundred cc. of clear fluid were found in the pericardial sac and 1500 cc. of clear fluid were noted in the pleural cavities. Pain and dyspnea were absent. A pericardial friction rub and the pulsus paradoxus were recorded as absent. The condition of the cervical veins and the position of the patient were not noted. Roentgen ray and electrocardiographic examinations were not done.

Summary of Group D. Six Cases of the Postmortem Series of Pericardial Effusions Correctly Diagnosed Clinically. Of these 6 cases correctly diagnosed there were 4 males and 2 females. Four of the

cases contained 100 to 250 cc. of fluid in the pericardial sac and pericarditis was present in each instance. There were 2 cases with 500 cc. or more of fluid; 1 of these cases had pericarditis while the other did not. Two cases had acute rheumatic pericarditis, 2 cases pericarditis associated with infection, 1 had polyserositis and 1 had chronic passive congestion. Four cases had over 500 cc. of pleural effusion, which was clear or slightly turbid in all cases. The pericardial fluid was as follows: bloody, 2; purulent, 2; serofibrinous, 1; and clear, 1. Pain was present in 2 cases, and dyspnea in 5. A pericardial friction rub was heard in 3 cases. The pulsus paradoxus was noted once and 3 patients assumed the orthopneic position; the cervical veins were noted as distended in only 1 instance. Heart sounds were poor or distant in 2 cases; murmurs were present in all cases. The electrocardiogram of the 1 case with more than 500 cc. of pericardial fluid was interesting in that it showed low voltage. Correct Roentgen ray diagnosis was made in 1 of the 3 cases having 100 to 250 cc. of pericardial fluid; it was questioned in the 1 case with over 500 cc. which was radiographed. Three of the patients were acutely ill and 3 were chronically ill.

E. Cases of Pericardial Effusion from Eye and Ear Service. This small group is composed of 1 female, 72 years of age, and 1 male, 23 years of age. The former had a streptococcus pericarditis associated with otitis media; the latter had a streptococcus pericarditis associated with mediastinitis and laryngeal edema. In the former case there were 100 cc. of purulent fluid and in the latter 200 cc. of serofibrinous fluid. Pain was present in the latter case. The presence or absence of dyspnea was not noted. There was no mention of any of the following signs: position of patient, murmurs, cervical veins, heart sounds, pulsus paradoxus. A pericardial friction rub was noted as present in the latter case but not mentioned in the former. The Roentgen ray report on the latter case in which were found 200 cc. of fluid was as follows: "Very broad superior mediastinum." The clinical diagnosis of effusion was not made in either case. In the case which had 200 cc. of fluid the diagnosis of "Pericarditis" was made but the opinion offered regarding effusion was: "No signs of effusion." Both patients were acutely ill and medical consultants saw both of them.

Group II. Pericardial Paracentesis Cases of Pericardial Effusion Without Postmortem Examination. This group is composed of 15 clinical cases with the diagnosis of pericardial effusion definitely established by the removal of fluid from the pericardium, either by a simple paracentesis with trocar or by more complicated operations. Twelve of these cases were taken from the records of the general services of the Massachusetts General Hospital and represent the number of such cases from January 1, 1920, to February 1, 1931. Three of the cases were taken from our private case records.

There were 14 males and 1 female. The youngest was 9 months old and the oldest 46 years. The ages by decades were as follows: first, 4; second, 4; third, 2; fourth, 4; and fifth, 1.

Etiology. Five of the 15 cases had acute rheumatic pericarditis, 2 had tuberculosis of the pericardium, and there was 1 case each of the following: questionable rheumatic pericarditis, Streptococcus viridans endocarditis complicating rheumatic heart disease, Staphylococcus aureus infection with osteomyelitis, Streptococcus hemolyticus infection, pneumococcus infection Type I, postscarlatinal infection, purulent pericarditis due to an unknown organism, and probable polyserositis.

Pericardial Fluid. The amounts removed by tapping were as follows: less than 100 cc. in 3 cases, 100 to 250 cc. in 5; 250 to 500 cc. in 2, and 500 cc. or over in 5. In 1 of these last 5 cases in which there was a constant drainage tube inserted the exact amount drawn off was not known but by means of a postmortem paracentesis 650 cc. were obtained. The character of the fluid in the 15 cases was as follows: clear, 1; "amber," 4; serofibrinous, 2; serosanguineous, 1; bloody, 2; turbid, 2, and purulent, 3.

Symptoms. Pain was present in 9 cases and noted as absent in 2. Dyspnea was present in 13 cases and absent in 2.

Signs. Pericardial friction rubs were heard in 12 cases and noted as absent in 1 case. Ten cases presented murmurs; 5 had no murmurs. The heart sounds were distant in 11 cases, fair in 3, and good in 1. A pulsus paradoxus was noted as present in 8 cases. The cervical veins were noted as distended in 4 and normal in 1, whereas 9 patients were in the orthopneic position and 2 were able to lie flat.

Radiographic Examination. Thirteen of the 15 cases were examined by Roentgen ray. A correct diagnosis was made in 12 cases and the diagnosis of pericardial effusion was questioned in the other case.

Electrocardiograms were done in 3 of these patients but showed nothing of value in helping to confirm or to deny the diagnosis of effusion.

Course. Seven cases died while under close observation; 8 cases were discharged improved but 1 of these died suddenly soon after. One of the cases has since returned to the hospital and is included as 1 of the 2 cases on which a cardiolysis was done. Microscopic sections of the pericardium in this case are suggestive of tuberculosis.

One of the most interesting and instructive points in this group was that 650 cc. of fluid were obtained by paracentesis in 1 case immediately after the patient died. In this case on previous paracentesis only a small amount of fluid was obtained, which makes us believe that the other cases also had much larger amounts of fluid than were obtained on tapping the pericardium, and in fact a much

larger amount of fluid than is usually stated to be necessary to produce signs and symptoms sufficient to establish the clinical diagnosis of pericardial effusion.

The case which presented a combination of constricting pericarditis and pericardial effusion calls our attention to the problem from a somewhat different angle. Here the amount of fluid found in the pericardial sac was not of great quantity (Fig. 1) and yet the patient showed marked signs and symptoms of cardiac embarrassment due to extrinsic factors and, as the pericardium was definitely thickened and acted as a constrictor of the heart, we may assume that this factor rather than the fluid was the cause of the signs and symptoms in this patient.

Clinical Diagnosis. The correct clinical diagnosis was made in all of the 15 cases.

Treatment. Therapy in these cases of pericardial effusion consisted in the first place of paracentesis, often with considerable relief. Sometimes the tapping was repeated. Almost always as much fluid as possible was withdrawn, without harmful effects. Otherwise symptomatic therapy was carried out as needed, with salicylate treatment in the rheumatic cases and a recommendation for sanitarium treatment in the case of the tuberculous patients. Cardiolysis was done in 2 cases and a pericardiotomy in 2 others. Oxygen was injected into the pericardium in 1 case after fluid was removed (Figs. 2 and 3) and this procedure was repeated three times over an interval of 2 months. From 200 to 600 cc. of oxygen were introduced each time after a larger amount of fluid was withdrawn. In spite of this procedure the pericardium later contracted and had to be resected at operation 5 months later. Perhaps the procedure of therapeutic pneumopericardium was not continued sufficiently long in this case—an interval of 6 to 12 months might have proved more successful.*

Summary. We have presented herewith (1) the pertinent clinical and pathologic data on the 126 cases containing over 100 cc. of pericardial fluid found at postmortem examination at the Massachusetts General Hospital over a period of 10 years (1921 to 1930, inclusive), this number occurring among 95,542 cases admitted to the hospital and among 1729 necropsies (7.3 per cent); (2) similar data collected from the Massachusetts Eye and Ear Infirmary, in a series of 71,334 admissions and 109 necropsies, 2 cases (1.83 per cent) showing 100 cc. or more of pericardial fluid; and (3) the clinical data on 15 cases in which pericardial paracentesis established the diagnosis of pericardial effusion.

I. The postmortem group was divided into (A) cases with 100 to 250 cc. of pericardial fluid, (B) cases with 250 to 500 cc., and (C)

* The individual case reports which have been omitted here for the sake of brevity are included in the authors' reprints.

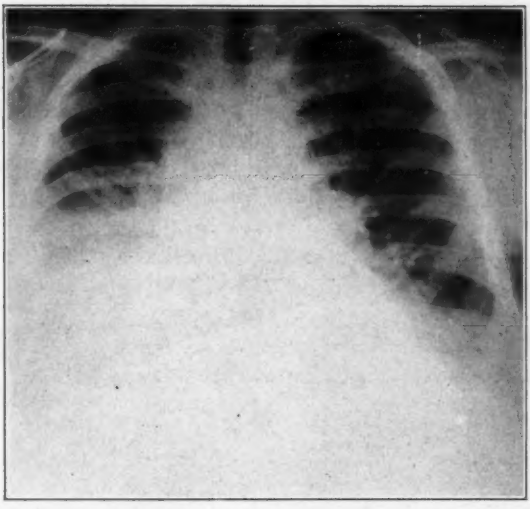

FIG. 1.—Roentgen ray picture of heart and pericardial shadow of J. B., Case 14 of the pericardial paracentesis cases. In this case there was a small pericardial effusion restricted in amount by a much thickened constricting pericardium (proved at operation). There was also fluid in both pleural cavities. Tuberculous pericarditis.

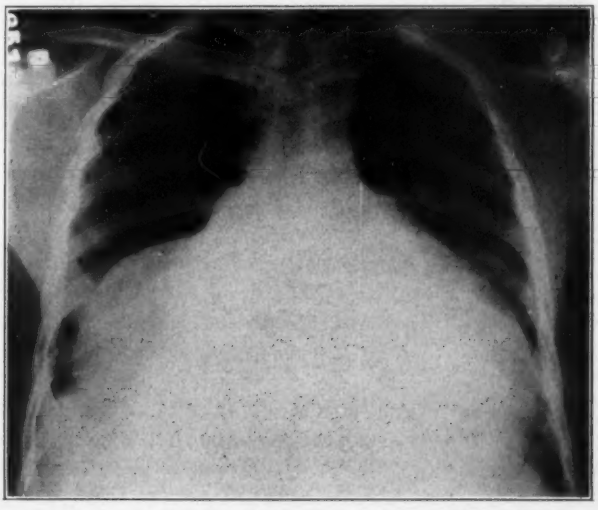

FIG. 2.—Roentgen ray picture of the enormous pericardial effusion of L. A., Case 15 of the pericardial paracentesis cases. Tuberculous pericarditis.

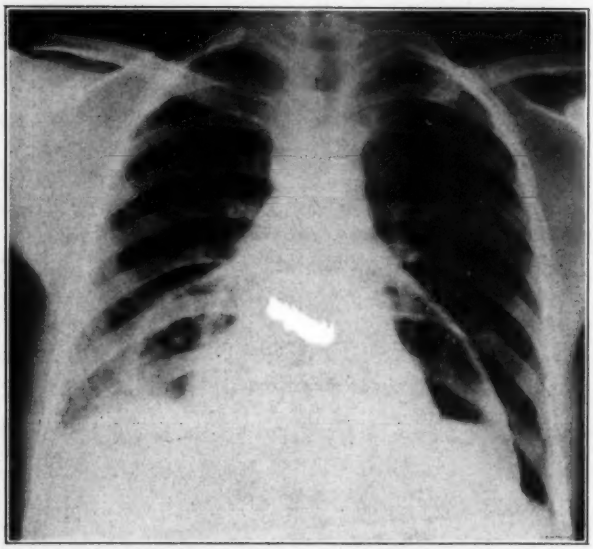

FIG. 3.—Roentgen ray picture, showing oxygen and fluid in the pericardium of L. A., Case 15, whose pericardial effusion before paracentesis was shown in Fig. 2. The oxygen was introduced as a therapeutic procedure.

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cases with 500 cc. and over. These were subdivided into cases with pericarditis, without pericarditis, and with new growth. Class A contained 94 cases: 72 without pericarditis, 21 with pericarditis, and 1 with new growth. Class B contained 24 cases: 20 without pericarditis, 2 with pericarditis, and 2 with new growth. Class C contained 8 cases: 5 without pericarditis, 1 with pericarditis, and 2 with new growth. There were 2 cases from the Eye and Ear Infirmary, both of which had pericarditis and less than 250 cc. of fluid.

Etiology. The predominant etiologic factor in the cases with pericarditis was infection of some type (uremia was a rare cause). In cases without pericarditis the predominant etiologic factor was chronic passive congestion or infection elsewhere in the body, with some question as to the mechanism of the production of the pericardial effusion.

Symptoms and Signs. Pain was present in 24 of the 126 cases of the postmortem series of the Massachusetts General Hospital, dyspnea in 68, orthopnea in 37, distended cervical veins were noted in 5, pericardial friction rub in 8, distant heart sounds in 29, and the pulsus paradoxus in 1 case.

Radiography. Forty-nine cases were examined by Roentgen ray. A correct diagnosis was made once and questioned in 3 other cases. Allowances must be made because many of these cases were examined at least several days before death and often in a very sick condition, with pleural fluid sometimes obscuring a part of the heart shadow.

Clinical Diagnosis. Of the 126 cases of the postmortem series at the Massachusetts General Hospital a correct clinical diagnosis was made only six times. Four of these 6 had pericarditis with an effusion of 100 to 250 cc. Two had an effusion of over 500 cc., 1 with and 1 without pericarditis. The diagnosis of effusion was questioned in 1 case with 100 to 250 cc. without pericarditis. Here again the same allowances must be made as in the case of the Roentgen ray diagnosis just cited.

II. The clinical group of 15 other cases in whom a pericardial paracentesis established the diagnosis of pericardial effusion was most instructive since it was made up of patients who presented the classical signs of effusion in a much greater degree than did the "postmortem" cases.

From 1 of these cases 650 cc. of fluid were obtained by a pericardial paracentesis immediately postmortem, while during life paracentesis had yielded a much smaller amount. Since this case presented signs and symptoms similar to the others in this group and since even larger amounts of fluid were obtained in others we believe that almost every one of these clinical cases had over 500 cc. of pericardial fluid.

Another interesting case in this group was that one in which there was a chronic constrictive tuberculous pericarditis to which was added an acute or subacute pericardial effusion. Here the amount of fluid was small but it was sufficient when added to the already constricted pericardial sac to cause grave clinical signs and symptoms.

Conclusions. From the above data we conclude that without the presence of an acute fibrinous pericarditis, the diagnosis of pericardial fluid is likely to be missed unless the effusion amounts to over 500 cc.

To establish a clinical diagnosis of a pericardial effusion all signs and symptoms must be very carefully looked for and analyzed and Roentgen ray studies employed in all cases except a very few where the effusion is so large and rapid in its development that the clinical diagnosis is easily made at once.

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NONFATAL STAB WOUNDS OF THE VENTRICLES.

WITH ELECTROCARDIOGRAPHIC SIGNS OF CORONARY THROMBOSIS AND ABSENCE OF ANGINAL PAIN.*

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WOUNDS of the ventricular musculature with and without injury to one of the major branches of the coronary arteries have been reported in considerable numbers in current medical literature. The electrocardiographic changes noted by observers using this method of study have been similar in essential details to those seen in acute coronary thrombosis. It has been our good fortune to have for study 2 patients with stab wounds of the ventricles, 1 involving the left ventricular musculature and a branch of the left coronary artery and the other the right ventricular musculature, but with no injury to a coronary vessel. Both patients were treated surgically and each patient has been followed sufficiently long to note his complete clinical recovery.

The electrocardiograms are of interest in that the changes are marked and are produced by lesions, the location and extent of which are definitely known. It is reasonable to assume that the heart muscles were normal before the accident, for neither patient gave a history indicating any previous disease liable to produce heart muscle pathology, and their youth and general physical survey precluded the existence of any degenerative vascular disease.

In 1 instance a coronary artery was tied and in both instances muscle tissue was enmeshed by suture material producing a lesion somewhat similar in character to a small myocardial infarction. In each instance the operation was performed under local anesthesia which permitted accurate notation of subjective phenomena. It is of peculiar interest to note that in neither case was pain of an anginal type noted during or following the procedure.

This report is presented not only to place on record wounds of the heart treated surgically with recovery, but particularly to record the clinical behavior of the patients, noting the absence of pain in heart lesions with electrocardiographic changes similar to those

* Read at the Meeting of the American Climatological and Clinical Association, Atlantic City, May 5, 1932.

observed in coronary occlusions and produced probably by myocardial changes of the same fundamental nature.

Case Reports.* CASE 1.—W. R., negro, male, aged 23 years, was admitted to the St. Philip Hospital, October 2, 1930, at noon. He had been stabbed in the left side of the chest about thirty minutes before admission. He later stated that he walked 1½ blocks after being stabbed before he began to feel faint, and estimated that 10 to 15 minutes elapsed

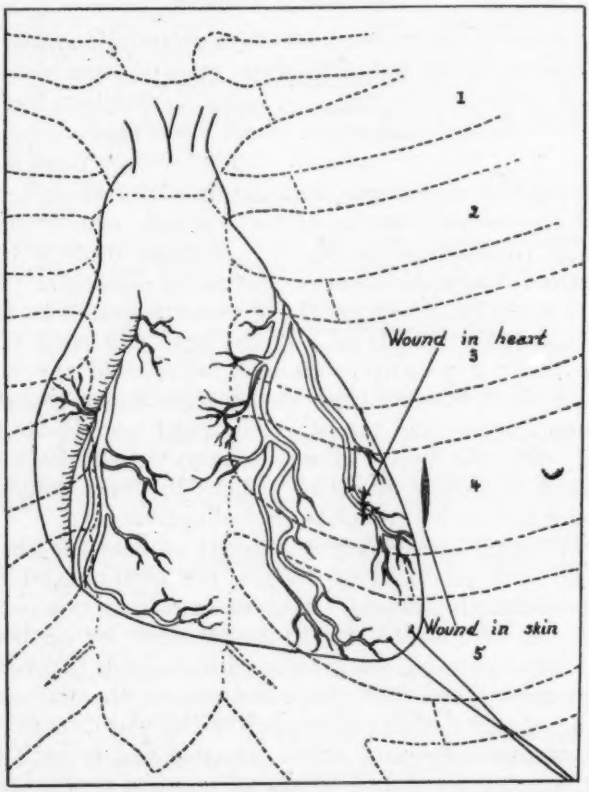

FIG. 1.—Case 1. The approximate location and size of the wound in the left ventricle and the severed coronary vessel.

between the time of injury and the appearance of marked weakness. When first examined in the hospital he appeared to be in profound shock. The radial pulse was not detectable and his blood pressure was not obtainable. Examination of the chest showed a stab wound in the fourth intercostal space, 5 cm. to the left of the sternum. The heart sounds were distant and muffled and the cervical veins were full. These signs were thought to indicate hemopericardium with cardiac tamponade. An operation was deemed urgent and was performed under local infiltration

* A detailed report of the surgical aspects of these cases will appear in the Proceedings of the Southern Medical Association for 1931.

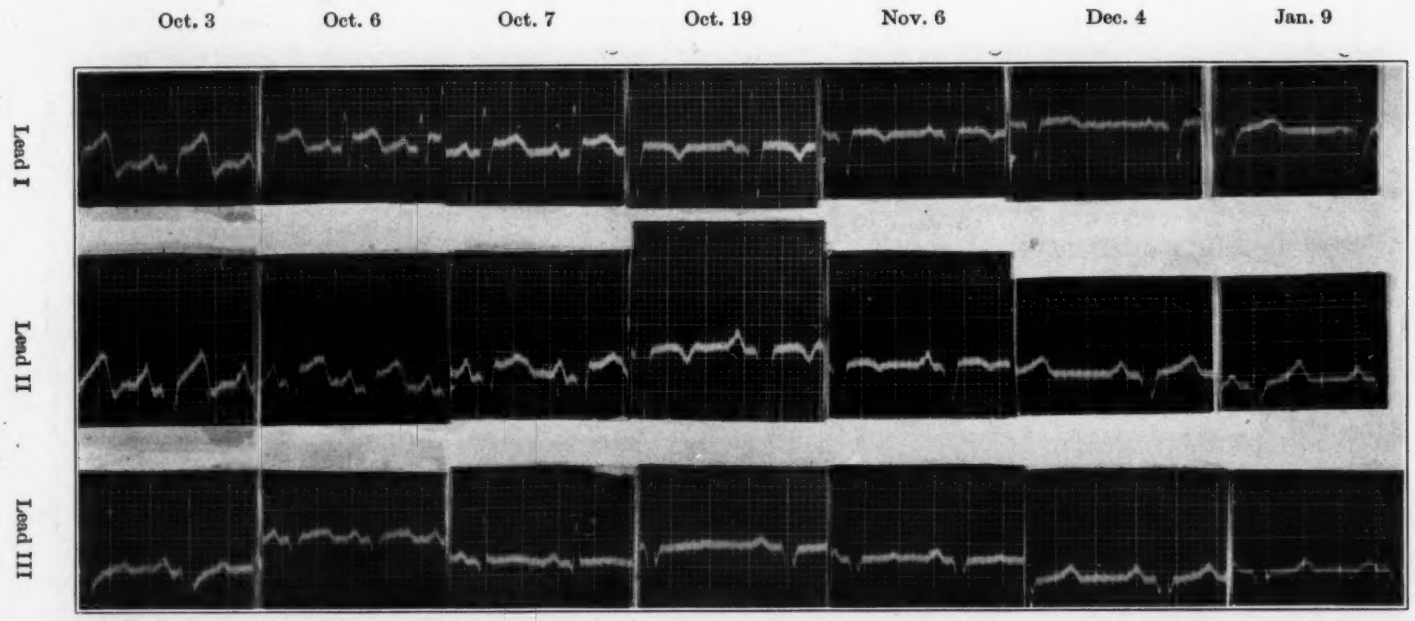

CHART I.—Case 1. The first electrocardiogram was made 14 hours after the operative repair of the wound. The changes noted are characteristic of those seen in coronary thrombosis. The electrocardiogram of January 9 shows a complete return to normal.

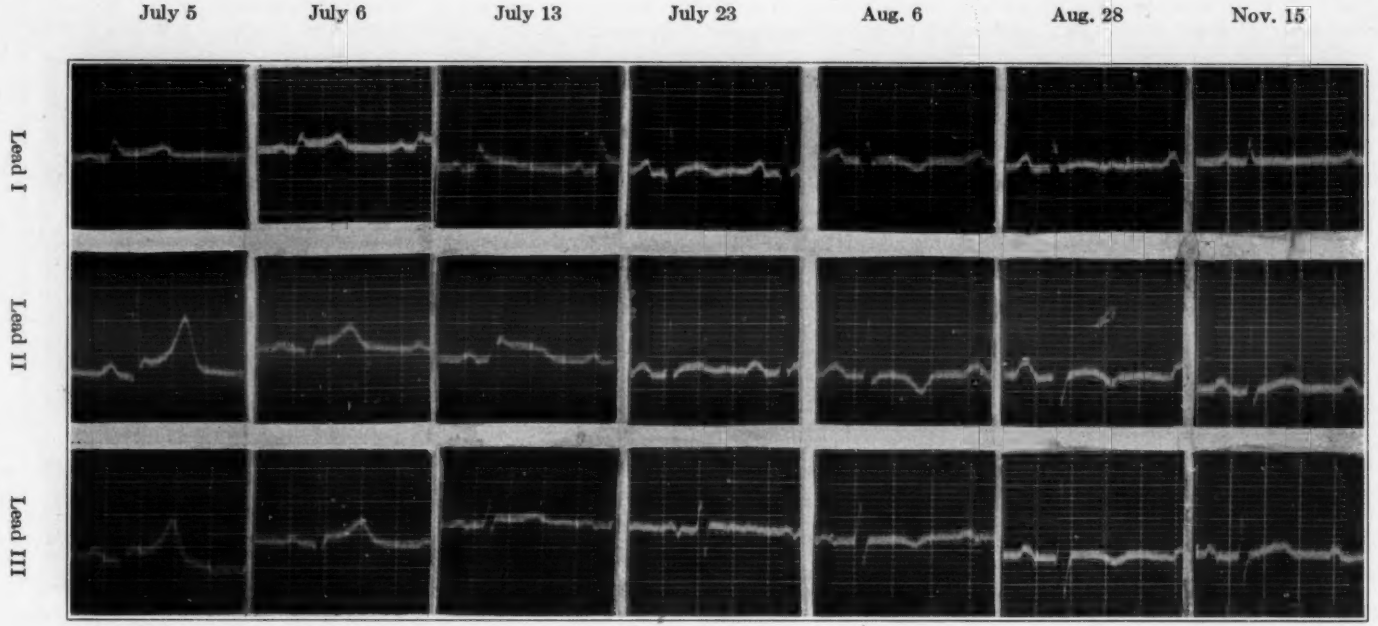

CHART II.—Case 2. The first electrocardiogram was made 9 hours after the operative repair of the wound. The changes noted are characteristic of those observed in coronary thrombosis involving this area of the heart muscle.

anesthesia. When the pericardium was incised more than 200 cc. of blood were evacuated and bright red blood was found to be spurting from a wound in the left ventricle. A wound, 1 cm. in length, was found on the left border of the heart (Fig. 1) parallel to its long axis and about 5 cm. from the apex. The descending branch of the left circumflex coronary artery had been divided. The wound was closed with three interrupted sutures and the bleeding artery ligated. Incision of the pericardial sac had produced a prompt improvement in the pulse rate and volume.

The patient was discharged in good condition 16 days after the injury. Seen in April, 1931, he stated that he was doing routinely the work of a laborer. At that time physical examination, electrocardiographic and Roentgen ray studies of the heart revealed no phenomena indicative of cardiac disease. Chart I illustrates the electrocardiograms taken while in the hospital and since his release.

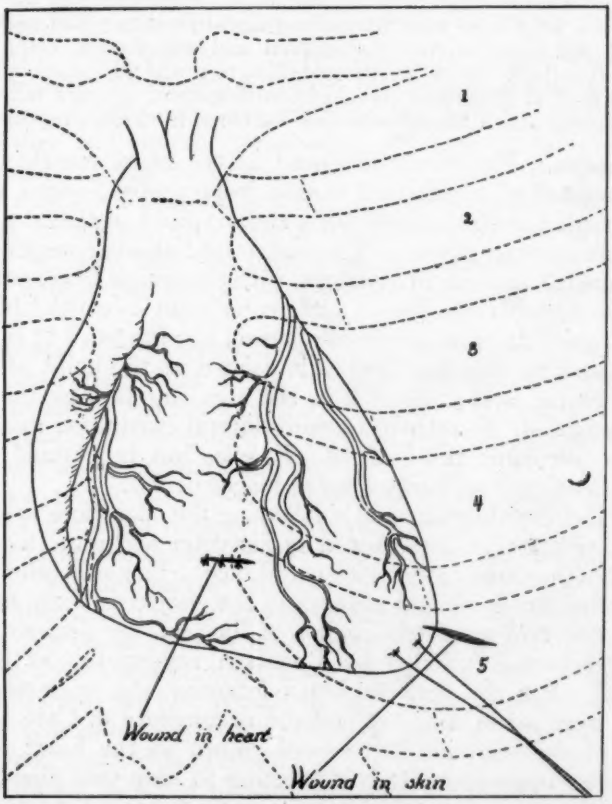

FIG. 2.—Case 2. The approximate location and size of the wound in the right ventricle.

CASE 2.—W. J., negro, male, aged 36 years, entered St. Philip Hospital at 11 P.M., July 4, 1931. He stated that he had been stabbed in the chest with a pocket knife about 7 P.M., after which he ran about 50 yards and fell to the ground unconscious. He was put in a car and carried 5 miles to a physician who noted that the patient was bleeding freely from the chest

wound and was in profound shock. He was given morphin and atropin and placed on a table with his feet elevated. In about 15 minutes the pulse became palpable and the skin warm. The patient was brought 20 miles to the hospital and when admitted his systolic blood pressure was 112 mm. Hg. and pulse rate 90 per minute. A stab wound was noted 5 cm. from the midsternal line in the fifth intercostal space. The area of cardiac dullness was not definitely increased, but the heart sounds were distant and muffled. A diagnosis of stab wound of the heart was made from the history with suggestion of a cardiac tamponade, which had probably been relieved by the free bleeding from the chest wound. The operation was performed under local infiltration anesthesia. Only a moderate amount of blood was found in the pericardial sac, but there was a constant flow of dark blood from a transverse wound 1.5 cm. in length in the midportion of the anterior wall of the right ventricle, about 5 cm. above the apex level. (Fig. 2.) The wound was closed with three interrupted sutures of fine silk. The patient's course in the hospital was uneventful, except for a mild local staphylococcic wound infection. The patient has been followed since leaving the hospital and was studied completely 7 months after the accident, all studies failing to reveal any pathologic aftermath. Chart II illustrates the electrocardiographic changes noted while in the hospital and 2 months after his discharge from the surgical service.

Discussion. The lesion produced in the heart muscle in each case consisted of a puncture wound from a sharp-edged weapon which divided cardiac muscle fibers and in Case 1 sectioned a branch of the left coronary artery. The end result following surgical repair was an area, 1 to 2 cm. in diameter, with the muscle fibers enmeshed in suture material and drawn sufficiently tight to control bleeding, and in Case 1 the injured coronary vessel was ligated. It is reasonable to assume that local ischemia existed at the point of the repaired wound, and in Case 1 in the area supplied by the artery which was tied. In each instance collateral circulation might conceivably overcome the induced ischemia, but this would require several hours and probably a much longer period.

The electrocardiograms made following the operations are similar in every respect to those noted in coronary occlusion, and probably have the same pathologic significance. The only other logical explanation for significant changes in the electrocardiograms would be the effect of an accumulation of fluid in the pericardial sac. This factor was excluded by Roentgen ray studies at frequent intervals. For the first few days following the operation these studies were made daily. Fluid did accumulate in Case 1 to the extent of embarrassing the venous return to the heart eighteen hours after operation. It is interesting to note that changes previously observed in the electrocardiograms remained constant after the fluid was evacuated by opening the wound, yet all phenomena of cardiac tamponade were promptly relieved.

The infrequent assocation of cardiac pain with wounds of the heart muscle is of peculiar significance. In the 2 cases here presented pain of anginal type was entirely absent at any period before, during or after operative repair, and the operation was done with

the use of a local anesthetic injected only in the chest wall. Neither patient was sufficiently ill at the time of the operation or afterward to modify his perception or consciousness of pain. It may be profitable, therefore, to consider the significance of the absence of pain in heart muscle wounds, especially those involving the coronary vessels as related to the pathogenesis of cardiac pain in angina pectoris.

Keefer and Resnick[1] have recently reviewed completely the accumulated evidence dealing with the various factors concerned in the pathogenesis of angina pectoris. They contend that the most tenable hypothesis is that this syndrome is related directly to conditions which induce ischemia of the heart muscle, and that the pain of coronary thrombosis is of the same fundamental nature. They comment upon the interesting clinical fact that the pain of myocardial infarction tends to subside with the development of heart muscle degeneration and eventually disappears entirely. Sutton and Lueth[2] have recently presented experimental evidence, which they feel proves conclusively that myocardial ischemia is fundamental in the production of cardiac pain.

The studies of MacWilliam and Webster[3] on the sensory phenomena associated with defective blood supply to the working muscle indicates that the pain of ischemia occurs only when the muscle is exercised under conditions inducing inadequate oxygen supply.

Lewis and his coworkers[4] in their studies in intermittent claudication have shown that the pain in this syndrome is due to a substance generated during muscle contraction which accumulated to a concentration sufficient to induce pain and remains stable in the tissue spaces during circulatory arrest.

Angina pectoris occurs in those patients in whom contractile power of the heart muscle is better preserved and frequently disappears when congestive heart failure supervenes. This would indicate that the pain is caused by a substance dependent upon muscle contraction under special conditions, for those factors which induce pain do so by increasing heart muscle work. If one transfers the recent observations made on the mechanism of pain in skeletal muscle to the wounds of heart muscle here studied, one finds a reasonable explanation for the absence of pain, although heart muscle ischemia existed.

The wound in either of the cases presented consisted primarily of a severance of the muscle fibers extending in depth the entire thickness of the heart wall. The area of ischemia resulting from repair of the wound, which in one involved the placing of a ligature on a coronary artery, embraced an area of heart muscle which had been so injured by the penetrating weapon that normal contraction could not occur. The pain producing metabolites which form during muscle contraction and accumulate in the tissue spaces to a concentration sufficient to induce pain were therefore not produced,

though absolute or relative circulatory arrest existed. That the absence of pain was due to a rapid relief of ischem a by collateral circulation is not tenable. The nature of the lesion and subsequent changes in the electrocardiogram indicate that an injury to the heart muscle similar in nature to that occurring in coronary thrombosis was induced by the wound and operative repair.

If the absence of pain in patients with penetrating wounds of the heart muscle, who have as a result of the wound and operative repair an area of myocardial ischemia, is here given the correct explanation, it logically follows that certain aspects of angina pectoris are accounted for. The angina pectoris of effort is relieved by cessation of exercise, for the degree of myocardial ischemia is insufficient to allow the pain producing substance to remain in the tissue spaces in sufficient concentration, under the conditions of reduced rate of formation consequent upon body rest. The pain of coronary occlusion with acute ischemia in the infarcted area of heart muscle gradually lessens with the development of muscle degeneration and finally ceases when this has developed to a degree incompatible with muscular contraction.

These observations emphasize the importance of myocardial ischemia as a fundamental factor in the mechanism of angina pectoris, but at the same time suggest that heart pain will not occur if the ischemic area involves muscle tissue degenerated sufficiently to impair its contractile power.

A case reported by Burian[5] of a wound of the heart which severed a branch of the left coronary artery, but involved only superficial layers of the heart muscle, has a direct bearing on the cases under consideration. His patient following the repair of the wound, which consisted mainly in tying the bleeding vessel, had postoperative anginal pain which he stated was a troublesome symptom. The anginal attacks were attributed by him to an area of heart-muscle anemia. In the light of recent data and the cases here studied it would appear logical to assume that the origin of pain was due to the contraction of heart muscle under ischemic conditions, the superficial nature of the lesion not interfering with this function in the area supplied by the severed vessel. This case is contradictory to the observations of Sutton and Lueth[2], for they noted that pain was not produced in dogs if the continuity of the vessel or the adventitia was broken.

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THE USE OF BACTERIOPHAGES IN WOUND INFECTIONS AND IN BACTEREMIAS.*

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During a study of filterable viruses in 1915 Twort[1] observed in his cultures of smallpox vaccine a curious progressive dissolution of bacterial colonies. By transfer of material from the location on the plate, where a colony had dissolved, to the edge of a normal bacterial colony, he was able to initiate the lytic process in the latter situation and to continue such transmission from colony to colony in series. Twort regarded the phenomenon as a transmissible disease of bacteria, most probably caused by a filterable virus. Subsequent writers have contributed an abundant discussion in regard to the nature of bacteriophage, without adding materially to the original conception of Twort. d'Herelle[2] subsequently observed a similar phenomenon in cultures of the Shiga bacillus, particularly when derived from the intestinal contents of patients recovering from bacillary dysentery. He was able to transmit the filterable agent from culture to culture and to use it with success in the treatment of dysentery by administering it to the patients. Subsequent investigators have been able to recognize a large number of these filterable agents which are capable of bringing about the destruction of different kinds of bacteria. Of particular interest is the bacteriophage active against the staphylococcus which has been studied by Gratia.[3] The results of recent investigations offer some hope that it may be possible to find agents of this sort which are effective against many of the various bacterial causes of disease.

The Nature of Bacteriophage. The question as to the nature of bacteriophage cannot be adequately answered at present. We are not in a position to say exactly what filterable viruses are, although most bacteriologists are inclined to regard them as living beings. The bacteriophage certainly shows many characteristics which are similar to those of filterable viruses and many are inclined to agree with Twort that the bacteriophage should be classed as a filterable virus. This view, however, is disputed by some, who are inclined to regard the bacteriophage as some sort of an enzyme which is liberated upon the disintegration of the bacteria.

Combat of Infections With Bacteriophage. The use of bacteriophage in the treatment of infectious diseases was suggested by Twort, but

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he found no opportunity to undertake such a study. d'Herelle has been the chief exponent of such practical use. In general, one must recognize that the problem presents a somewhat different aspect, depending upon the location of the infectious process. When the infecting microbes are growing upon epithelial surfaces or in the tissues very close to the surface the application of the bacteriophage can be made directly. In such a disease as bacillary dysentery the microörganisms ordinarily penetrate only a short distance into the tissues and the bacteriophage may be introduced into the intestinal lumen and thus reach the bacteria. Infections of the urinary tract with colon bacilli present a somewhat similar relationship. Although these bacteria may sometimes penetrate deeply into the substance of the kidney or even reach the blood stream, they tend in most instances to remain on the epithelial surface or in the immediately adjacent tissues. Infections of the nasal mucous membrane and the nasal sinuses behave in a similar way. In applying the bacteriophage to disease of this sort one is ordinarily able to reach the bacteria without introducing the bacteriophage into the blood stream or the lymph spaces.

When one approaches the treatment of infections more deeply situated in the tissues of the body, the problem is complicated by the necessity of applying the bacteriophage in the presence of the living tissues by passage through the lymph or the blood. One might assume that the bacteriophage would exhibit its characteristic effect upon the bacteria in such a situation just as it does upon the agar plate or in the broth culture in the test tube. Such, however, is not the case. Numerous studies, some of which have been carried out in our own laboratory, clearly indicate that the combat between the bacteriophage and the bacteria is profoundly influenced by the presence of various environmental factors. In particular we may mention such things as the presence of blood,[4] of blood serum and of purulent exudate, the chemical reaction of the media,[5] the presence of various antiseptics and the temperature. In the combat against these internal infections the presence of purulent exudate and of blood can hardly be avoided. One can hardly expect, therefore, that the bacteriophage will destroy the bacteria in a dramatic fashion when the combat takes place in the interior of the body. In fact our experience in this field has persuaded us that the bacteriophage has a much less marked effect in such cases and that it may succeed merely because it produces a slight alteration in the bacterial bodies so that they are rendered more susceptible to the ordinary defensive mechanisms of the body, such as the phagocytic leukocytes. It is evident that much more detailed studies will be required before we fully understand the events which take place in an inflammatory lesion under treatment with bacteriophage in the interior of the body.

Clinical Applications. The principal interest of this audience doubtless concerns the application of bacteriophage in the treatment of particular clinical entities, and I have chosen to speak more especially of our experience with infected surgical wounds and bacteremias. The application of bacteriophage to the treatment of furuncles and carbuncles[6] seems to be on well-established basis. We advise that the staphylococcus bacteriophage be introduced into the lymph spaces about the boil through a very fine needle, and that this injection treatment by multiple punctures be repeated after about 48 hours. A considerable experience with furuncles and carbuncles has led my associates and me to the opinion that lesions of this sort due to staphylococcus should be treated with bacteriophage routinely. We recognize, however, that boils get well when treated in various ways and, on this account, any new method of treatment may not rapidly replace other procedures. It does seem, however, that the surgical excision of carbuncles might well be delayed until bacteriophage has been given a trial.

Infected wounds, whether accidental or surgical, have been treated by bacteriophage in several instances with good success. When the infection is chiefly by Staphylococcus aureus, local applications of dressings wet with the staphylococcus broth bacteriophage filtrate usually bring about rapid improvement. The purulent exudate is washed away, healthy granulations appear and the wound proceeds to prompt healing.

A more difficult situation is presented by those wounds which are continually reinfected by intestinal contents. We have had to deal with instances of this sort in which an operative incision in the abdominal wall has become soiled with intestinal contents by perforation of the intestine, recognized some time after the surgical operation. Such fistulous tracts have been treated by application of large amounts of mixed bacteriophage preparations, including bacteriophages active against staphylococcus, colon bacillus, dysentery bacilli and Bacillus pyocyaneus. In 2 instances the patients have done very well and the surgeons have expressed themselves as surprised at the success of the treatment.

Bacterial infections of the blood stream[7] present a much more serious problem. In these one is practically always dealing with a pure culture of bacteria. We have had most experience with infections of this type due to the staphylococcus. When blood stream infection is a sequel of a local staphylococcus wound infection we recommend application of large quantities of the bacteriophage to the surface of the wound. At the same time, however, the intravenous injection of the bacteriophage is undertaken. For this purpose we employ a special filtrate prepared in a culture medium without protein and containing asparagin as the important source of nitrogen. This bacteriophage preparation does not of itself produce serious toxic symptoms in animals and it seems to be far less

dangerous to the patient than is the filtrate of broth culture. Staphylococcus bacteremia is a disease with high mortality and one does not undertake its treatment without recognizing that failure will be commonly met with. We have, however, had an opportunity to observe some instances of actual recovery after repeated positive blood cultures in staphylococcus bacteremia.

As a sequel to bacteremia one meets with metastatic localizations of the inflammatory process. Here we may mention especially osteomyelitis[8] which is so common in children, inflammation of the pericardium and localization on the endocardium. The treatment of these localizations by bacteriophage presents very serious difficulties, which we have so far not been able to overcome and at present it seems that here surgical drainage when applicable will, as a rule, be required in order to offer any hopeful outlook for bacteriophage therapy.

Specificity of Bacteriophage. Some physicians think that the bacteriophage is a single agent and that the same bacteriophage may be employed against various infecting bacteria. This is unfortunately not a correct idea. It is true that some of these lytic agents are capable of attacking two or more related kinds of bacteria such, for example, as the Shiga bacillus and the Flexner bacillus of dysentery. Such polyvalency is, however, not the rule. One finds that the colon bacillus can grow actively in the bacteriophage broth filtrate active against staphylococcus. As a rule, therefore, an accurate etiologic diagnosis is necessary before one can apply bacteriophage therapy with hope of success. We do not insist that bacteriologic cultures are necessary before one can begin treatment. Certainly some diseases, such for example as furunculosis, can be diagnosed with considerable accuracy as to etiology, so that treatment may be begun while waiting for the cultures to develop. It is necessary to emphasize that bacteriophage is not a general antiseptic. As a matter of fact, the bacteriophage preparation is a good culture medium for bacteria other than the particular organisms against which the bacteriophage is potent.

Incompatibilities of Bacteriophage. It also seems important to emphasize the incompatibility of bacteriophage therapy. This agent should be employed under conditions which favor its action and offer it at least a reasonable opportunity to attack the bacteria. On epithelial surfaces, therefore, it is important that the chemical reaction of the medium should be suitable. The presence of chemical germicides or antiseptics seriously interferes with the action of the bacteriophage. It is also necessary to recognize that inflammatory exudates, blood serum and blood itself interfere with the efficiency of this agent. We have met with considerable difficulty in impressing the importance of these considerations upon some of our clinical associates who have been interested in combining bacteriophage therapy with other procedures.

A few records of individual patients have been selected for brief mention in order to illustrate the character of our experience.

Clinical Notes. CASE 1.—A man, seen in 1929, with repeated positive blood cultures, staphylococcus abundant in urine and in sputum, was given bacteriophage subcutaneously and into the nephrectomy wound after removal of a large abscessed kidney. The pneumonia cleared and the infectious process in the second kidney gradually subsided. After a prolonged convalescence the patient returned to work and continues well.

CASE 2.—A physician developed sepsis early in 1930 after surgical removal of ureteral calculus. Blood culture repeatedly showed staphylococci in small numbers. Bacteriophage was poured into the wound. Subsequently the blood culture became negative for staphylococcus. After a prolonged convalescence, complicated by vertebral osteomyelitis, the patient has returned to the active practice of surgery.

CASE 3.—A boy, aged 15 years, with positive staphylococcus blood culture, temperature 104° to 105° F., and symptoms of early osteomyelitis and pericarditis, was given large intravenous doses of the asparagin bacteriophage; 40 cc. on January 31, 1931, and 74 cc. on February 2, 1931; a total of over 900 cc. during the course of the illness, which terminated in death on February 24. Blood cultures taken after February 2 remained negative, but the pericardial exudate contained living staphylococci at the end.

CASE 4.—A boy, aged 12 years, with about 50 staphylococci per cc. of blood, was operated upon for acute osteomyelitis of right femur and right tibia. During the following 6 days he received the equivalent of 80.3 cc. of undiluted asparagin bacteriophage in divided doses. Blood culture taken shortly before death from massive pneumonia, on the sixth day, was still positive for staphylococcus.

CASE 5.—A physician, aged 24 years, with a furuncle on upper lip and cellulitis of face, temperature 104.6° F., had a negative blood culture taken, December 6, 1931, at 9 P.M. Immediately thereafter bacteriophage was injected intravenously. Temporary improvement was followed by extension of the process. Blood culture, taken December 8, 1931, showed about 170 colonies of staphylococcus per cc. of blood. Local injections of bacteriophage into the facial tissues were given on December 8. The patient died, December 11.

CASE 6.—A young woman showed Bacillus coli in blood culture following septic abortion, with temperature up to 106° F. The pelvic condition was considered inoperable. Intravenous bacteriophage injections produced frightful reactions. The blood culture became negative in 3 days and the patient recovered completely after several weeks in hospital.

CASE 7.—A woman, aged 34 years, developed fecal fistula after removal of an inflamed papillary cyst from the pelvis. Irrigation of the sinus with a mixture of various bacteriophage preparations was followed by amelioration of symptoms and slow convalescence. The patient has returned to work.

The very brief recital of these cases may be misleading and may cause you to think that bacteriophage therapy is a dramatic, sudden and decisive remedy for severe infections. I prefer rather to regard it as a helping hand, which sometimes seems able to tip the balance in favor of recovery of the patient. Greater clinical experience may make possible a more intelligent use of these agents with, possibly, an improvement in results.

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OBSERVATIONS ON THE EFFECTS OF OXYGEN THERAPY. II. CHANGES IN THE CIRCULATION AND RESPIRATION.*

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Measurements of the circulation and respiration, similar to those already reported in the literature and summarized in our first report,[1] were made as part of the study of the effects of oxygen therapy. These determinations were undertaken to serve not only as a quantitative check of the clinical observations but also to attempt to determine whether they were simply a measure of the clinical condition and varied with the clinical course or, on the other hand, whether they were dependent on the use of the oxygen-rich atmosphere and were therefore in part responsible for the clinical changes noted.

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In order to evaluate these alternatives, observations were made, not only on 6 cardiac patients, but also on subjects who might serve as controls—2 patients with pneumonia, 4 with hyperthyroidism, 1 young diabetic, and 2 healthy individuals. The "noncardiac cases" served, in a way, as a control. As far as possible the observations during oxygen treatment were controlled in each case by determinations during a period before and after the oxygen treatment. The management of the patients was first stabilized and remained unaltered unless the condition became progressively worse during oxygen treatment. The measurements included in the present report will deal with (1) vital capacity, (2) breath-holding, (3) minute volume of respiration, (4) heart rate, (5) arterial blood pressure, (6) venous blood pressure, and (7) the electrocardiogram.

Measurement of Respiration. The minute volume of respiration was determined by measuring the volume of expired air collected in a small spirometer (Sanborn vital capacity model). A two-way flap valve was used to direct the expired air into the spirometer. A three-way stopcock in the line was employed to connect and disconnect the patient with this spirometer. The connections were made and broken at the beginning of an inspiration, the time of collection being noted with a stopwatch; from these data the minute volume of respiration was then calculated. The vital capacity was measured in the usual way. The "breath-holding" time was determined after a normal inspiration, the patient being instructed to stop breathing as long as possible.

In Table 1 are assembled the data of the more completely studied cases. It was not always possible to get complete data, because of the clinical condition, especially in the cardiac patients. The minute volume of respiration in the cardiac patients paralleled the clinical course. The decreased breathing did not precede the other evidence of improvement when improvement occurred. It is interesting to note that in 3 of the 4 hyperthyroid patients and in both of the normal patients a decrease in minute volume of breathing was noted in the oxygen atmosphere; this was associated with a decrease in depth rather than with a diminution in rate. Furthermore, these alterations were associated with only slight changes in arterial oxygen saturation and in one of the normal cases (LK) with no change at all (*cf.* our other report[2]). Apparently some other mechanism besides relief of arterial anoxemia is at least partly responsible for the decrease in breathing. The possibilities exist that the oxygen-rich environment alters the blood in some way, viz., by a tendency toward an alkaline pH, and so depresses the respiratory center, or that the stay in a high oxygen environment sets up reflexes from the alveoli to depress breathing. The increase in CO_2 content of the arterial blood (*cf.* our other report[2]) may be in part due to the decrease in breathing. The improvement in breathing is appar-

TABLE 1.—ANALYSIS OF DATA.

Patient and condition.	Breath-holding, sec.	Vital capacity, liters.	Minute volume of breathing, liters per min.	Arterial blood pressure, mm. Hg.	Venous pressure.	
					Direct, mm.H_2O.	Indirect, mm.H_2O.
LK—Normal						
Before O_2	59	3.5	10.0	108/58	15	40
During O_2	51	3.4	6.8	108/70	70	10
After O_2	43	3.4	8.0	112/72	35	110
SS—Normal						
Before O_2	84	3.6	5.7	102/70	150	90
During O_2	113	3.8	5.6	100/70	110	110
After O_2	76	3.7	4.5	98/68	90	..
PI—Thyroid						
Before O_2	7	1.9	6.1	146/70	100	110
During O_2	11	1.6	4.4	140/86	55	..
After O_2	7.5	2.0	5.3	160/90	..	95
RA—Thyroid						
Before O_2	23	1.3	9.8	210/110	..	70
During O_2	45	0.9	7.6	208/116	20	..
After O_2	21.5	1.3	9.0	198/104	60	100
SCH—Thyroid						
Before O_2	33	2.9	5.4	108/70	80	100
During O_2	19	2.7	3.4	110/72	..	60
After O_2	19	2.5	6.0	108/66	40	40
CO—Thyroid						
Before O_2	15	1.9	..	128/70	75	80
During O_2	22	1.5	7.2	110/68	..	60
After O_2	14	1.6	7.5	126/64	75	80
BR—Cardiac						
During O_2	17	2.3	27.7	117/74	90	95
	35	1.8	8.1	140/86	10	25
	17	1.5	11.4	132/88	150	..
After O_2	24	2.1	17.9	158/80	30	50
BER—Cardiac						
Before O_2	13	1.4	3.9	150/92	150	..
During O_2	20	1.1	3.1	130/90	..	60
Out of O_2	24	1.1	4.7	118/90	140	150
During O_2	12	1.1	3.2	170/92	125	90
After O_2	17	1.3	8.0	140/80	..	..
GE—Cardiac						
Before O_2	21	..	..	120/80	..	..
During O_2	25	..	..	120/80	..	..
	33	..	..	110/74	..	..
After O_2						
BA—Cardiac						
Before O_2	5	1.0	8.0	140/80	70	..
During O_2	6	0.8	8.0	140/96	35	50
After O_2	4	0.6	..	160/90	..	..

ently easily masked when the clinical course of the patient is progressively downgrade in oxygen; for example, one case (BA) while in oxygen showed no improvement in breathing due apparently to the associated progression of the decompensation.

The slowing in breathing was not accompanied by an increase in vital capacity in the cases in which the latter was measured, but in most cases by a slight but definite decrease in vital capacity (Table 1). This occurred also in the 3 cardiac cases in whom a complete set of observations of vital capacity were made. The decrease in minute volume cannot therefore be ascribed to an alteration in vital capacity, since it occurred when the vital capacity was unchanged or actually decreased slightly.

The length of time the breath was held was increased in practically all the "noncardiac cases" in which this item was studied and also in most of the cardiac cases, sometimes even when the patient became clinically worse. The test, however, is not entirely satisfactory in patients because the psychic element is a variable which seems to be a large factor in determining the time of breath-holding. Furthermore, the breath should be held longer in oxygen since the alveolar oxygen content is higher than in ordinary atmospheres and the stimulating effect of asphyxia on breathing therefore would be delayed. This extra store of oxygen in the alveoli while in an oxygen-rich environment may be of importance in preventing or minimizing an unsaturation of arterial blood which might otherwise ensue during quick adjustment to extra demands of the body tissues for oxygen.

Measurements of Circulation. The ordinary auscultatory method was used for estimating arterial blood pressure. Venous pressure was measured by Eyster's[3] indirect method and by a direct method modified from Moritz and Tabora.[4] The latter consists of an adjustable 1-cc. pipette, (*Pp*) Fig. 1, mounted on a millimeter rule (*S*) and connected by a T-tube (*TT*) to a needle adaptor (*A*) and a 21-gauge needle to be inserted into the vein. The other connection of the T-tube is to a small separatory funnel (*SF*); small stopcocks (*SC*) having been placed in the rubber tubing leading from the T-tube to the needle and in the tubing leading to the reservoir, so that the pipette can be separated from the reservoir and connected to the needle in the vein or *vice versa*. The apparatus is sterilized before using and filled with sterile physiologic saline solution. The pipette is made movable on the mm. ruler so that it can be shifted until the level of fluid is stationary. In this way, movement of blood into the needle and movement of saline into the vein are minimized. As a check, to assure the patency of the needle, the pipette is shifted slightly to see if the fluid returns to its original level. The level on the scale is read and corrected for the zero level of the right auricle. Tests showed that the indirect method did not always check with the direct, differing by as much as 60 mm.

of H_2O (Table 1). For these reasons it seems to us the direct method is more satisfactory than the ordinary indirect method and no more complicated. It deserves to be used more than it has been in the past.

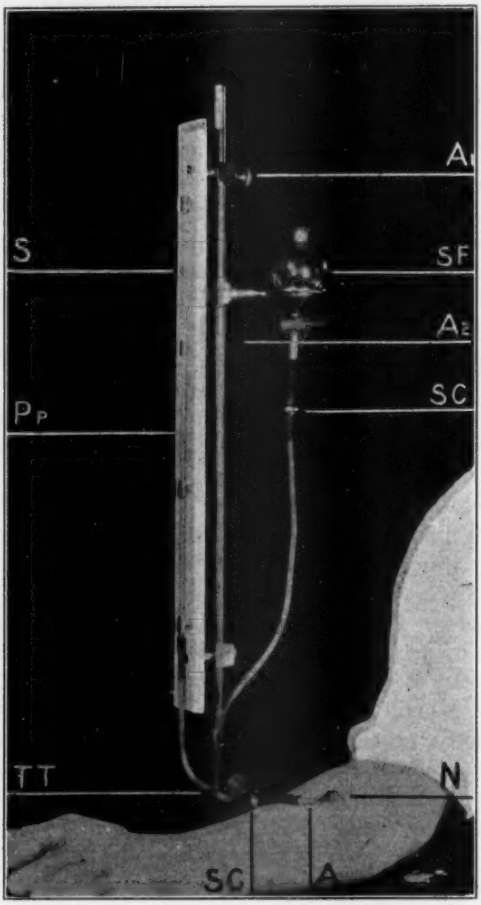

FIG. 1.—Apparatus for direct venous pressure determinations, *S*, millimeter rule with clips for pipette; *Pp*, 1-cc. pipette; *TT*, T-tube; *SC*, stopcock; *A*, adaptor; *N*, needle; A_2, rod of stand, *SF*, separatory funnel; A_1, clamp holding rule on stand

The changes in heart rate were measured by one of us in the ordinary way and checked by the electrocardiogram. The water intake and output were charted in all these patients.

No significant changes in arterial blood pressure were observed in these cases while in the oxygen-rich environment (Table 1). Nor were the changes in venous pressure significantly correlated with oxygen treatment, the changes being within the range of variation

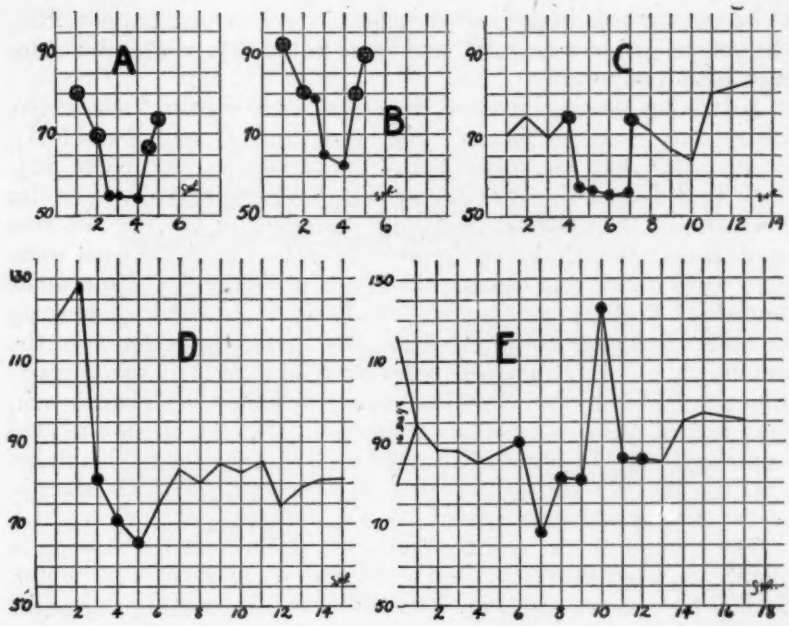

FIG. 2.—Pulse rate curve. *A*, *B* and *C*, controls; *D*, pneumonia; *E*, hyperthyroidism. ⊙, in oxygen room with normal oxygen content; ●, in oxygen-rich atmosphere; other points in ordinary air, outside oxygen room; ordinates, pulse rate per minute; abscissæ, days.

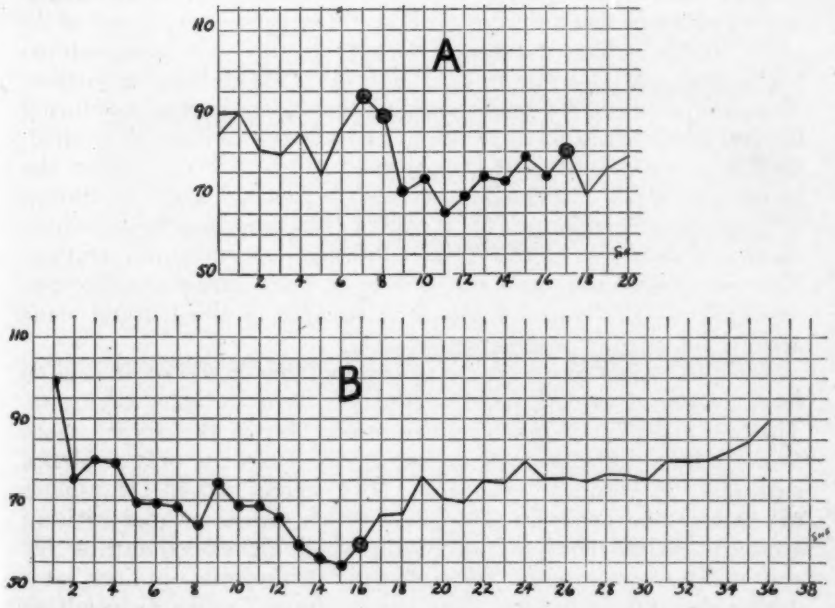

FIG. 3.—Similar to Fig. 2. *A*, hyperthyroidism; *B*, arteriosclerotic heart, recent coronary occlusion and heart failure.

to be encountered in such observations. In 1 cardiac patient (BR) the venous pressure dropped, and while in the oxygen chamber later rose again temporarily.

A striking slowing of heart rate was noted in the "noncardiac cases" during oxygen therapy (Figs. 2 *A*, *B*, *C*, *D*, and *E* and 3 *A*). A similar slowing was noted in 1 of the cardiac patients (BR) (Fig. 3 *B*), but not in the cardiac patients having persistent auricular fibrillation. This slowing might be the result of an effect exerted upon the sinus node by environmental factors in the oxygen room and tent. How this change is initiated, whether by some reflex from the alveoli or by changes in the blood, is not clear. There can be no doubt that slowing the heart rate and the diminution of the minute volume of respiration are beneficial actions of oxygen therapy which in themselves, and aside from any relief of arterial anoxemia, may help to turn the downward course of the cardiac case toward improvement. In cases with fibrillating auricles it is significant that the benefit of oxygen therapy may be lessened by the absence of the slowing of the ventricles.

The changes in the electrocardiogram, aside from the slowing in sinus rate when fibrillation of the auricles was absent, were minor. In Fig. 4 are shown segments of the electrocardiogram from a patient (*RA*) with hyperthyroidism taken before (*A*), during (*B*), and after (*C*), a stay in the oxygen room. The slowing in rate during oxygen therapy is evident. In this case, as in several other of the "noncardiac" and cardiac patients, the *T* wave became larger and longer in two or more leads during the stay in oxygen, *i. e.*, 9 out of 13 cases studied. The increase in this particular case was confined to Leads I and II while in Lead III the *T* wave became smaller. The amplitude of *QRS* increased in all three leads in this case during oxygen administration, as occurred in 10 of the 13 cases so studied. In Fig. 5, curves obtained on a normal subject (SS), is shown the increase in *QRS* amplitude especially in Leads I and III, during oxygen administration. This is one of the exceptional cases which showed a decrease in the *T* wave during oxygen administration. The record does not show the slowing in pulse rate during oxygen so clearly as the chart of Fig. 2 *A* because of the marked sinus arrhythmia present in this person.

An interesting series of electrocardiograms is shown in Fig. 6 from a case of cardiac failure (BR) due to a coronary occlusion. The first record (*A*), taken on the second day in the oxygen room shows a large Q_3 and small inverted cove T_3 as the only evidence suggestive of coronary occlusion. The second record (*B*), shows the paroxysmal auricular fibrillation which was associated with an apparent second coronary occlusion which developed during his stay in the oxygen room. The following two records obtained later during the stay in oxygen show low "voltage," probably resulting from the second coronary attack. The striking slowing of the heart

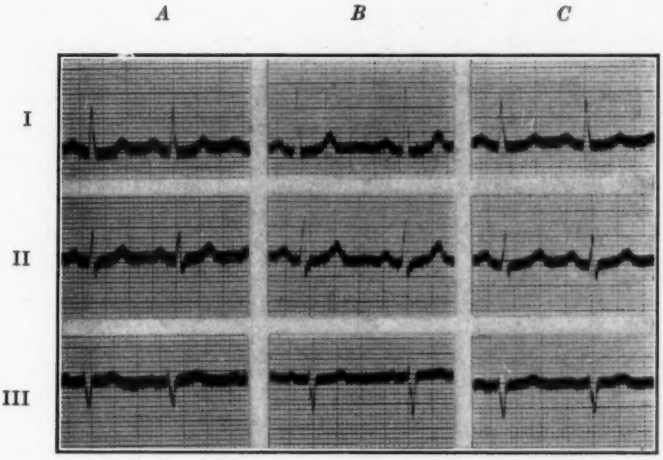

FIG. 4.—Electrocardiograms, three standard leads, on normal individual, whose pulse rate is shown in Fig. 2 *A*, taken before (*A*), during (*B*) and after (*C*) administration of oxygen.

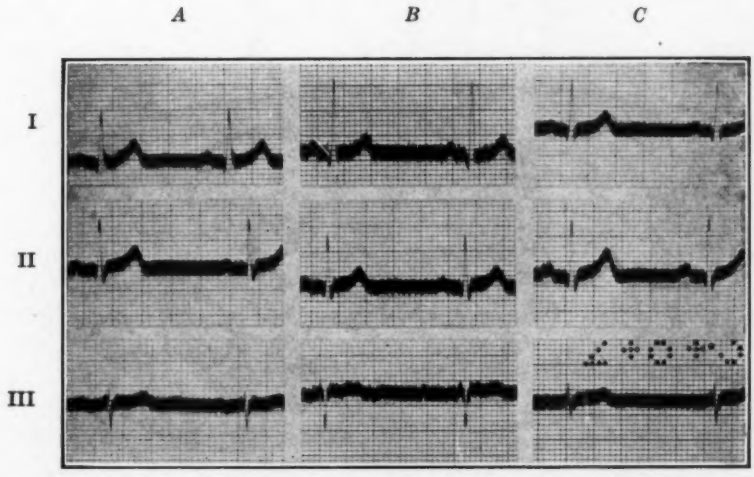

FIG. 5.—Electrocardiograms, three standard leads, on patient with hyperthyroidism, taken before (*A*), during (*B*) and after (*C*) administration of oxygen.

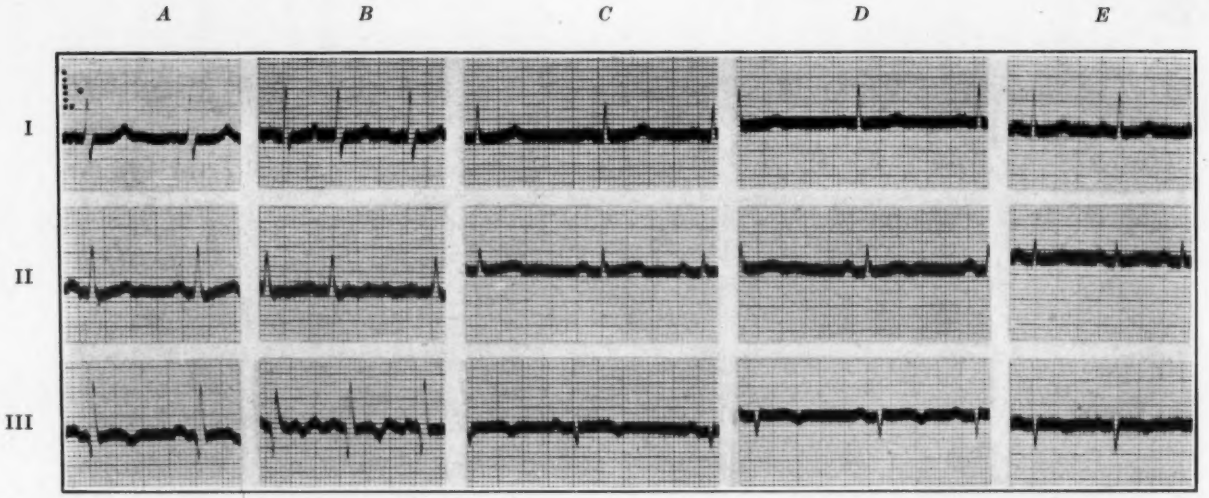

FIG. 6.—Electrocardiograms, three standard leads, on cardiac patient whose pulse rate is shown in Fig. 3 *B*. Curves *A*, *B*, *C* and *D* were taken during oxygen therapy, curve *E* after removal from oxygen room.

rate in this patient while in oxygen is seen by comparing the two records (*C* and *D*) with the last of the series shown (*E*), taken after the patient had left the oxygen chamber.

No diuretic action could be demonstrated in any of the "noncardiac" patients while in the oxygen chamber. This was also true in those cardiac cases which did not show any striking improvement in oxygen. A decrease in edema and diuresis was, of course, found in the cardiac patients as one of the concomitants of clinical improvement, but the study of the "noncardiac" patients and normals would indicate that the diuretic action which Barach[5] has stressed is a result of the improvement in the condition of heart and circulation and not, apparently, a direct diuretic action of the high oxygen environment. In the cardiac cases which became worse clinically during oxygen administration the edema and the oliguria increased.

Summary and Conclusions. A comparison of the effects of oxygen therapy on the circulation and respiration of a group of cardiac and "noncardiac" patients was used as a check on the clinical impressions, and to determine whether these changes preceded, accompanied or followed the clinical improvement.

A modified direct venous pressure method is described, and also a simple clinical method of determining minute volume of respiration.

Oxygen therapy tended to decrease the vital capacity slightly. It caused no significant changes in arterial and venous pressure.

An increase in the amplitude of *QRS* and an increase in the size and duration of the *T* wave was found in the majority of cases during exposure to an oxygen-rich atmosphere.

Oxygen therapy was found to result in (1) a slowing of the heart by causing a sinus bradycardia, (2) a decrease in minute-volume of respiration, and (3) an increase in the length of time the breath could be held. These changes tend to occur as readily in the "noncardiac" case as in the cardiac, and in the latter in spite of advancing failure. These changes are primarily the result of the oxygen-rich environment and seem in part, at least, independent of relief of arterial anoxemia. These changes in heart rate, in breath-holding ability and in minute-volume of respiration are in themselves beneficial and may be ways, aside from relief of arterial anoxemia, by which oxygen therapy may act beneficially in cases of heart failure. No slowing of ventricular rate occurred in cases with auricular fibrillation, and less beneficial effects may be expected from oxygen therapy in such cases.

No direct diuretic action was observed as a result of oxygen, either in the edematous or nonedematous patients.

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OBSERVATIONS ON THE EFFECTS OF OXYGEN THERAPY. III. BLOOD CHEMICAL CHANGES.*

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Exposure to atmospheres containing higher percentages of oxygen than the 21 per cent present in air at sea level has been reported to be of therapeutic value in many conditions in which anoxemia is a feature; this applies particularly to conditions like pneumonia and cardiac failure in which the poor oxygenation is due mainly to decreased aëration of the blood in the lungs. These findings have been reviewed in a previous report.[1]

Barach,[3,4,5] who devised tents and rooms for the efficient administration of oxygen, has made a number of clinical and chemical studies of patients during the treatment. We have undertaken similar studies, using both oxygen tents and two oxygen rooms, and have in general confirmed the earlier work. We have, however, included normal subjects in our series, and patients with emphysema and exophthalmic goiter—conditions not hitherto reported—who also served as controls, although in a more limited way.

The clinical observations of the effects of the treatment on respiration and the circulation have been presented elsewhere.[1,2]

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This paper is confined to the report of the chemical findings in the arterial blood of our subjects. In each case the blood was investigated for: (1) Oxygen content and capacity (the ratio of content to capacity giving the percentage oxygenation, normally about 95 per cent); (2) CO_2 content of the blood serum; (3) hydrogen ion concentration of the blood serum; (4) glucose, nonprotein nitrogen, urea, chlorids, cholesterol and lactic acid contents of whole blood.

This last group of findings showed no consistent variations that could be attributed to oxygen therapy, and are therefore omitted from the table of results (Table 1). Whenever possible, blood

TABLE 1.—BLOOD FINDINGS (ARTERIAL BLOOD).

Patient.	Date.	Per cent O_2 saturation.			CO_2 content.			pH.		
		Before O_2.	During O_2.	After O_2.	Before O_2.	During O_2.	After O_2.	Before O_2.	During O_2.	After O_2.
I.	April 3	92.5	..	..	51.0	..	..	7.50	..	..
Normal	5	..	96.0	..	..	53.0	..	..	7.45	..
S. S.	6	..	..	93.0	..	..	57.0	..	..	7.50
II.	April 3	95.5	..	..	46.0	..	..	7.40	..	..
Normal	5	..	95.0	..	..	50.0	..	..	7.40	..
L. K.	6	..	..	95.0	..	..	55.5	..	..	7.45
III.	Dec. 26	66.5	..	..	51.0	..	..	7.35	..	..
Lob. pneu.	29	..	69.5	..	..	62.5	..	..	7.40	..
Bo.	Mar. 19	..	..	94.0	..	..	49.0	..	..	7.55
IV.	Dec. 31	64.5	..	..	70.5	..	..	..	..	..
Broncho-	Jan. 2	..	94.0	..	..	94.5	..	..	7.40	..
pneu.	27	..	..	91.0	..	..	62.0	..	..	7.40
Nim.										
V.	Feb. 26	85.0	..	..	41.5	..	..	7.55	..	..
Cardiac	Mar. 5	..	92.0	..	..	42.5	..	..	7.50	..
Ba.	10	..	83.5	..	..	64.0	..	..	7.70	..
	17	..	..	90.5	..	..	76.5			
VI.	Jan. 31	94.5	..	..	44.0	..	..	7.30	..	..
Cardiac	Feb. 5	96.5	..	..	42.5	..	..	7.35	..	..
Ber.	26	81.0	..	..	40.5	..	..	..	..	..
	Mar. 5	..	91.0	..	..	38.0	..	..	7.55	..
	10	..	85.5	..	..	45.0	..	..	7.45	..
	16	..	..	90.0	..	..	40.0	..	..	7.55
	23	..	97.5	..	..	35.5	..	..	7.55	..
VII.	Feb. 24	..	92.0	..	..	34.5	..	..	7.50	..
Cardiac	Mar. 2	..	83.5	..	..	60.0	..	..	7.50	..
Bie.	9	..	92.5	..	..	57.5	..	..	7.50	..
	11	..	..	83.5	..	..	50.5	..	..	7.55
VIII.	Dec. 22	81.5	..	..	77.5	..	..	7.45	..	..
Emph.	26	..	88.5	..	..	91.0	..	..	7.50	..
He.	29	..	91.0	..	..	100.0	..	..	7.55	..
	Jan. 2	..	..	81.0	..	..	85.5	..	..	7.45
	Mar. 20	..	..	88.0	..	..	78.0	..	..	7.55
IX.	Mar. 16	89.0	..	..	48.5	..	..	7.40	..	..
Thyroid	18	88.0	..	..	44.0	..	..	7.45	..	..
Co.	24	..	94.0	..	..	50.5	..	..	7.45	..
	31	..	..	93.0	..	..	..	..	..	7.50
	April 1	..	..	92.5	..	..	45.0	..	..	7.50
X.	Feb. 13	87.0	..	..	..	..	..	7.60	..	..
Thyroid	20	90.0	..	..	53.5	..	..	7.50	..	..
Sch.	25	..	96.0	..	..	61.5	..	..	7.55	..
	Mar. 20	..	..	92.5	..	..	52.0	..	..	7.40
XI.	Feb. 13	92.5	..	..	43.5	..	..	7.55	..	..
Thyroid	20	..	97.0	..	..	64.0	..	..	7.65	..
Rav.	21	..	..	91.0	..	..	53.5	..	..	7.65

was drawn at least 3 times from each subject—before, during and after oxygen administration. The management of the patient, including the use of medication, was kept constant during the whole procedure unless the patient's condition was obviously growing worse despite the oxygen therapy. The condition of the patient, of course, was often an uncontrollable variable; some improving, others declining during the treatment.[1,2]

The blood was drawn from either the brachial or radial arteries. It was handled under oil throughout the analytical procedure to prevent the loss of gases and was kept at a low temperature to prevent decomposition. The oxygen content of the atmosphere in the oxygen chambers was maintained at 50 to 60 per cent, and the temperature and humidity were held at comfortable levels, at 70° F. and 30 per cent relative humidity.

When patients showed a low percentage of oxygen saturation of the arterial blood, *i. e.*, a decrease in the ratio of oxygen content to oxygen holding capacity, this was usually increased, often markedly so, by breathing atmospheres high in oxygen. A normal control, S. S., who had a slightly low saturation, 92.5 per cent, showed a rise to 96 per cent saturation, whereas control L. K., who entered the oxygen chamber with a saturation of 95 per cent, showed no increase. The oxygen administration also failed to affect the oxygen saturation of blood in our 1 case of lobar pneumonia (III). This has been shown to occur by Stadie[6] and by Binger and Davis,[7] who interpret their results as showing that in such cases there may be consolidated portions of the lung in which the circulation is unimpaired but in which the blood is never exposed to air containing alveoli, an opinion in which we concur. In such lungs the complete saturation of the blood passing through the unimpaired portions of the lungs would be insufficient to increase appreciably the total oxygen content of the blood in the peripheral arteries, since a large proportion of the blood might be passing through the consolidated portion and into the arterial system with no increase in oxygen content whatever. The situation is analogous to a congenital heart defect in which venous blood intermingles with the arterial.

In the patients suffering with cardiac disease several instances were noted in which the percentage oxygenation of the arterial blood increased at first, but decreased again as the heart failure progressed, despite the continued administration of oxygen.

The carbon dioxid content of the blood of all subjects, including the normal controls, was markedly increased during treatment with oxygen, and often remained above the original level for some time after the patient returned to his normal environment. These results are in accord with those of Campbell,[8] who found an increased carbon dioxid tension in the extracellular tissue fluids of animals subjected to an environment of air at several atmospheres

of pressure. Case VIII, a patient suffering from emphysema, is worthy of note. As is usual in this condition, she entered the oxygen chamber with the abnormally high blood carbon dioxid content of 77.5 volumes per cent, which value rose to the remarkably high level of 100 volumes per cent during oxygen administration.

In all subjects there was a general tendency for a drift of the hydrogen ion concentration of the blood toward more alkaline values during oxygen therapy, although several exceptions were noted.

Discussion. Similar qualitative chemical changes in the arterial blood accompanied oxygen therapy in all individuals studied, including the normal controls. The changes differed markedly in degree in various individuals and conditions, but always in the same direction, thus emphasizing the fact that the effects of oxygen therapy are exerted upon the patient, rather than upon the disease. The administration of oxygen must be regarded as treatment to relieve the arterial anoxemia.

In some of the patients with heart disease there occurred at times clinical retrogression, which was paralleled by a decrease in blood oxygen saturation despite oxygen administration. It, therefore, seems logical to conclude that the oxygen cannot be considered as acting on the underlying cause of the disease. The function of oxygen therapy is to give the patient the benefit of as high a blood oxygen saturation as possible, while other means are employed to attack the underlying disorder.

It is interesting to note that all the hyperthyroid cases and one of the supposedly normal controls showed a percentage oxygen saturation of the arterial blood below the limits usually considered to be normal. This may be explained, in the hyperthyroid cases at least, as being due to an excessively rapid passage of blood through the lungs in such patients. The rapid flow shortens the time of exposure of the blood in the lungs to the alveolar air (this has also been alluded to by Binger, Brow and Branch[9]). An abnormal resistance to the passage of oxygen through the alveolar wall, or a lowering of the oxygen carrying power of the blood due to some chemical change of the hemoglobin may cause such a decrease in saturation.

The CO_2 and pH changes observed by us are similar to those reported by others. According to the view generally accepted at present and recently summarized by Barach[3] they are to be regarded as secondary to respiratory changes produced by effects on the respiratory center. It must be pointed out, however, that Cullen *et al.*[10] have recently questioned this point of view.

Conclusion. The function of oxygen therapy is not to attack the underlying causes of the disease, but to give the patient the benefit of as high a blood oxygen saturation as possible. It is conceivable, as was pointed out in a previous report,[2] that some of the benefits

of oxygen therapy may be produced in other ways besides the improvement of arterial anoxemia. However, the major benefit of oxygen therapy is the increase in oxygen saturation of the arterial blood, thus relieving the arterial anoxemia and its effects.

NOTE.—We are indebted to Dr. S. H. Rubinfeld for his assistance in obtaining some of the blood samples.

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OVARIAN FOLLICLE HORMONE THERAPY IN OVARIAN INSUFFICIENCY AND THE MENOPAUSE.

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THERE exists at the present time considerable confusion as to the status of ovarian hormone therapy. Rational as ovarian substitution therapy may theoretically appear to be in some conditions, the actual results are rarely striking and often difficult to detect. To some extent this is due to the lack of an objective index of ovarian activity. To this must be added the uncertainty of determining when the case is one of a pure ovarian insufficiency and when it is an anterior pituitary dyscrasia. There is some very convincing evidence as to the efficacy of substitution therapy in experimental ovarian insufficiency in animals. Here, however,

one is dealing with pure physiologic insufficiencies and not with the complex clinical syndromes which are encountered in clinical cases. Then, too, the quantities of hormone usually administered to experimental animals are relatively much greater than those ordinarily given to humans.

There have appeared from time to time convincing reports of the effect of various preparations of the ovarian follicle hormone in conditions of ovarian insufficiency. However, after carefully weighing the evidence regarding the efficacy of such therapy, a committee of the Council of Pharmacy of the American Medical Association decided that, although certain ovarian preparations were shown to be physiologically active, and able to induce œstrus in spayed animals, their therapeutic activity in the human, and their clinical field of usefulness, had not been sufficiently defined.

Since the isolation by Allen and Doisy[1] of the active hormone from the ovarian follicle, scattered clinical reports have appeared in the literature regarding the efficacy of this hormone in clinical subjects. McClendon[2] described 2 carefully studied patients in which he induced menstruation with the follicular hormone. Pratt[3] reported a limited series of cases, which he considered to be true ovarian insufficiency, in whom he obtained beneficial results from the administration of a form of this hormone.

Hirst,[4] Frank,[5] Sevringhaus and Evans,[6] Brouha and Simonnet,[7] Mahnert,[8] and Zondek[9] have all given similar reports as to the beneficial effects of various preparations in a small series of cases. Novak[10] is pessimistic about such therapy because of the difficulties of obtaining a satisfactory index of treatment. He further argues that the bleeding induced by such a method is not true menstruation.

Because of this diversity of opinions, the average clinician is hesitant to thrust such treatment upon his patients, in spite of the frequency with which he encounters conditions which appear to be true ovarian follicular hormone insufficiency. In view of the rapidly accumulating experimental evidence of the value of various preparations of this hormone, it seemed advisable to study the effect of a known physiologically active preparation in a series of clinical conditions which were commonly regarded as being due to ovarian insufficiency, with a view to substantiating further the work of previous observers, to determine some idea of the necessary dosage in terms of Allen-Doisy units, and to eliminate, as far as possible, all question of any benefits which might occur, being due to coincident nonspecific therapy.

The patients used in the following experiments were all ambulatory clinic cases. Only intelligent, coöperative women were chosen. These were seen at regular intervals throughout the period of observation. Two types of cases were selected for treatment: (1) menopause and (2) primary amenorrhea. Of the 10 cases of

menopause 2 were artificial and 8 were natural. All were selected because of the severity of symptoms such as hot flushes, pruritus, headache and nervousness. Cases with complicating hypertension were not used. In the 10 cases of amenorrhea there was considerable variation as to type, but all were shown to be free from anatomic lesions of the genital tract. Although pituitary ovarian insufficiency is not well defined, and it is difficult to determine which is primarily at fault, it soon became apparent that this group of cases could be divided into two clinical types. The first of these two types was anatomically normal in appearance, whereas the second showed obesity, hypertrichosis with masculine distribution, coarse voice and short stubby fingers. The first type was regarded as simple ovarian follicle hormone insufficiency, whereas the second was considered as belonging to the anterior pituitary ovarian dysfunction syndrome.

The ovarian follicular hormone used was prepared according to Morrell's modification of the Allen-Doisy technique.[11] The unitage of each batch was checked in our own laboratory in spayed rats, by the vaginal smear method.[12] The hormone was administered by means of vaginal pessaries, as described by Powers, Vanley and Morrell,[13] and Allen and Baker.[14] The dosage used varied considerably. In general, the principles of beginning with an overdose and diminishing it to the physiologic one was used. This appears to require adjustment in each individual case. During the control periods pessaries of plain gelatin were used and the patients were not informed of the change. No medication, other than the specific hormone, was given throughout the course of the study.

Table 1 is a summary of the cases used in the experiment. An effort was made to make the evaluation of results as critical as possible.

TABLE 1.—SHOWING THE RESULTS OF TREATMENT WITH OVARIAN FOLLICLE HORMONE.

	No. of cases.	Good results.	Fair result.	Doubtful result.	No relief.
Menopause:					
Natural	8	3	3	1	1
Artificial	2	2			
Amenorrhea:					
Ovarian follicle insufficiency	5	4	1		
Anterior pituitary ovarian type	5	..	..	..	5

The following case abstracts have been selected as being typical of the various groups described in Table 1. Examples of protocols in which no results were obtained have been included, as well as those in which good therapeutic effects were noted.

Case Abstracts. Group A. Natural Menopause. CASE 1.—C. P. (Cornell Clinic, A69034), American, white female, single, aged 41 years,

was admitted to the experimental group, February 17, 1931, complaining of nervousness, hot flushes, headache and cessation of menstrual periods. The patient had always been healthy. She was a business executive and indulged in athletics. Menses began at the age of 13 years and were always regular until the summer of 1930, when they became irregular and finally ceased in July, 1930. There was a gain of 20 pounds in weight in the 6 months prior to February, 1931. Physical examination showed no abnormal findings. There was moderate overnutrition; weight, 136 pounds. Systolic blood pressure was 140 and the diastolic 90. Pelvic examination was negative. A diagnosis of menopausal syndrome of only moderate severity was made.

Treatment. On February 17 the patient began to use intravaginally 300 Allen-Doisy units of follicular hormone daily. This was continued until February 21. On February 22 what appeared to be a normal menstrual period occurred and lasted 1 week. During this time the patient lost 5 pounds in weight. No hormone was administered until March 10, when she began to use 40 units daily. This was continued until March 22. No bleeding occurred although the patient volunteered the information that she had less headache and no flushes during the period of medication. From April 7 until April 30, 40 units of the hormone were used daily. On May 1 uterine bleeding occurred and lasted for 5 days. Treatment was discontinued until May 26, when the 40 units daily were begun. Bleeding again took place on June 1. Treatment was discontinued. No period occurred in July. The experiment was terminated on July 2. The patient then weighed 122 pounds. She stated that she had more energy and was almost free from symptoms during the time period when she was using the follicular hormone. This patient was a highly intelligent individual and insisted that the benefit was not psychic.

A reply to a follow-up letter was received on December 16, 1931. The patient stated that she was without therapy during June and July. About July 15 she had a return of her symptoms, such as flushes, nervousness and headache. These continued until she began using the hormone again on August 22. A menstrual period occurred on August 28. She had continued to use approximately 200 units during the last week of each intermenstrual period. Under this régime she had remained symptom free and had had what she considers to be regular menstrual periods.

Result. Reëstablishment of uterine bleeding in a case of recent menopause with relief of symptoms and a loss of 10 pounds in weight after moderately large doses of ovarian follicular hormone. On discontinuing treatment during a control period the symptoms reappeared and monthly uterine bleeding did not take place.

Case 2.—P. H. (Cornell Clinic, A74075), Russian female, married, aged 48 years, was admitted to experimental group on February 16, 1931, complaining of hot flushes, and cessation of menses. The past history was negative. The menstrual periods were regular until 1928. They then were irregular for 6 months and ceased in 1929. Since that time she had had severe hot flushes, occurring every 20 to 30 minutes, and aggravated by excitement. There had been a gain of 20 pounds in weight during the past 3 years. Physical examination was normal except for a slight laceration of the pelvic floor. The systolic blood pressure was 140 and the diastolic 86. The diagnosis was menopausal syndrome, moderately severe.

Treatment. On February 24 the patient began to use 40 Allen-Doisy units of follicular hormone daily. On March 10 she volunteered the information that flushes were occurring less often; on March 24 the flushes occurred only 6 to 8 times per day and were much less severe. On March 24 blank gelatin pessaries were substituted for those containing the hormone. On March 31 the patient complained of increased severity and frequency

of the flushes; on April 4 she began using 40 units of the hormone every second day; on April 14 she again noted a decrease in the frequency and severity of the flushes. Treatment was continued until June 9. The flushes continued to occur every 6 to 8 hours but were not severe. No menstrual bleeding occurred. There was no change in body weight or blood pressure.

Result. Moderate relief of subjective symptoms only in a case of menopausal syndrome of 2½ years' duration. The general result of therapy was considered doubtful in this case, although the patient had so much symptomatic relief that she desired to continue the treatment after the termination of the experiment. An attempt was made to determine the condition of the patient on December 15, 1931, but she could not be found.

Group A. Artificial Menopause. CASE 3.—M. L. (Cornell Clinic, A70742), white female, single, aged 42 years, was admitted to the experimental group on December 2, 1930, complaining of severe hot flushes. The past history was negative until March, 1930. At that time the uterus and both ovaries were removed because of multiple cysts in the latter. The menses, which had been regular until the operation, did not occur after it. Two weeks postoperatively she began to have severe hot flushes which were accompanied by palpitation and sweating. These were so severe that she was forced to stop her work as a secretary. They occurred at intervals of from 1 to 2 hours. During September and October, 1930, she took 15 grains of dried ovarian substance daily without effect. Physical examination revealed a healthy looking, intelligent woman with no abnormal findings. The systolic blood pressure was 150 and the diastolic 86. The diagnosis was menopause, artificial, severe.

Treatment. On December 2, 1930, the patient began to use 40 units of the follicular hormone intravaginally daily. On December 16 no change in condition was noted. On January 7, after using 40 units daily for 1 month, she volunteered the information that she had for the past 3 or 4 days noted a striking change in her condition. The flushes were much less severe and were no longer accompanied by palpitation and sweating. On January 14 she complained of a fullness in her breasts. Examination showed both breasts to be firm and tender. The flushes now occurred only occasionally and were not troublesome. The dosage of 40 units daily was continued until March 3. The patient remained almost symptom free. There was no change in blood pressure or body weight. On March 3 blank gelatin pessaries were substituted for those containing the hormone. She remained free from symptoms until March 20, when she began to have a return of the flushes and felt much as she did before beginning treatment. On March 25 she began to use 40 units of the hormone every second day; on April 7 she reported that she was again free from symptoms. This dosage of 40 units every second day was continued until June 1. During this time the patient remained without symptoms and carried on with her work. On June 1 the dosage was reduced to 40 units every third day. This proved to be sufficient to keep her symptom free. On July 1, at the termination of the experiment, the systolic blood pressure was 160 and the diastolic 86. There was no change in weight. A letter was received from the patient on December 16, 1931, in which she stated that 80 units per week were necessary to keep her free from symptoms. On several occasions she had tried reducing the dose but found that the flushes began to occur each time this was attempted.

Result. Striking relief of symptoms occurred in a case of artificially induced menopause. A return of symptoms took place during a control period when the hormone was stopped. A follow-up letter 1 year after the beginning of the experiment elicited the reply that the patient was continuing the therapy and was still free from symptoms.

Group B. Amenorrhea, Ovarian Follicle Insufficiency Type. CASE 4.—J. K. (Cornell Clinic, A59059), English school girl, single, aged 16½ years, was admitted to experiment on December 2, 1930, complaining of weakness and the fact that she had never menstruated. The past history was negative. The patient had never been robust and had received careful medical attention all her life. From time to time she had taken large quantities of dried ovarian substance by mouth, with no evident effect. Physical examination revealed a normal looking, slightly undernourished girl. Nothing abnormal was found. The lungs were clear and an intracutaneous tuberculin test was negative. Rectal examination revealed a small uterine fundus and cervix. The diagnosis was amenorrhea.

Treatment. On December 2 the patient began using 40 units of ovarian follicular hormone every second day intravaginally. On December 5 uterine bleeding occurred and lasted until December 9. This was the first occasion on which the patient had noted any evidence of menstruation. She continued to use 40 units every second day. On January 6 a second period occurred and lasted until January 10. It was accompanied by some abdominal pain. The therapy was stopped at this time, and blank pessaries substituted. On February 10 no further periods had occurred. At this time 40 units every third day was begun. On April 16 bleeding began and lasted for 4 days. The same dosage was continued and another period occurred on May 17 and lasted for five days. On June 1 the experiment was terminated.

The patient's mother replied to a follow-up inquiry on December 2, 1931. From June until the end of September the patient used 40 units of the ovarian follicle hormone twice weekly. Menstrual bleeding continued to occur at regular intervals. In October the therapy was stopped and a period occurred during October and again in November. Her general condition remained satisfactory.

Result. Menstrual bleeding at regular intervals occurred for the first time in a girl, aged 16½ years, during the administration of 80 units of the ovarian follicular hormone every second day and ceased to occur when therapy was withheld, during a control period. After 10 months of treatment with the hormone, it was discontinued and regular menstrual periods occurred for 2 months after therapy was stopped.

CASE 5.—L. A. (Cornell Clinic, A25605), Russian female, married, aged 24 years, was admitted, November 11, 1930, complaining of gain in weight and irregular menstruation. General health had been good. Menstruation began at the age of 15 years and had always been irregular. Periods usually occurred once every 3 or 4 months, were accompanied by dysmenorrhea and were scanty. The last period was in September, 1930. The patient had been married for 3 years. Frigidity existed. No pregnancies had occurred, although the husband had been shown to have active spermatozoa and no contraceptives were used. There had been a gain of 20 pounds in weight during the past 2 years. Physical examination showed an overweight, healthy looking young woman. Nothing abnormal was found in the general physical examination. The uterus was of the infantile variety and the cervix was small. There was no hypertrichosis and the hair distribution was of the normal feminine type. Diagnosis was amenorrhea, of ovarian follicle insufficiency type.

Treatment. On November 25 the patient began to use 40 units of the ovarian follicular hormone daily. This was continued until January 25, 1931. In all, approximately 2400 units were used. No menstruation occurred, but on January 25 the patient had severe abdominal cramps of the variety which she always associated with her menstrual periods. On February 1 she began using 300 units daily. On March 3 a menstrual period began which lasted until March 10. The blood loss was copious

and there was considerable pain. The patient stated that this was the first time she had ever experienced a menstrual period of that duration. No treatment was given until March 24, when she again began to use 40 units of the follicular hormone daily. Slight bleeding occurred on April 21 and a normal period of 6 days' duration began on April 28. There was very little dysmenorrhea on this occasion. Therapy was stopped until May 20, when she began to use 40 units daily. A period occurred on June 2 and lasted 5 days.

On June 15 there was no change in the patient's physical condition except for a loss of 7 pounds in weight. Her mental attitude was very much improved.

In a follow-up interview on December 2, 1931, the patient stated that she continued to use 40 units of the ovarian follicle hormone daily for 10 days preceding the usual date of the onset of menstruation throughout June, July, August and September. During this time the menstrual periods continued to be regular and she lost weight steadily. For financial reasons she was forced to discontinue the therapy at the end of September. No menstrual bleeding had occurred since and she had begun to gain in weight.

Result. Regular menstruation appeared to have been established in a woman, aged 24 years, in whom menstruation had previously been grossly irregular. Approximately 12,000 units of the hormone were used before menstruation became established. Relatively small quantities apparently were sufficient to maintain the menstrual cycle once it was established. After 7 apparently normal menstrual periods therapy was stopped because of the expense and no periods occurred.

Group B. Amenorrhea, Anterior Pituitary Type. CASE 6. — D. S. (Cornell Clinic, A69345), Russian female, aged 16 years, was admitted to experimental group, November 25, 1930, complaining of short stature and absence of menstruation. The child was normal at birth but had always grown slowly. The parents were normal. During the past year she had gained 15 pounds in weight. No menstrual periods had occurred. Physical examination showed a short, obese person, height 50 inches and weight 86 pounds. The fat was evenly distributed. The hands and feet were relatively small and the fingers were short. Body hair was sparse. Rectal examination revealed an infantile type of uterus and cervix. No other gross physical abnormalities were present. The diagnosis was anterior pituitary ovarian dysfunction.

Treatment. From November 26, 1930, until February 15, 1931, the patient used 40 units of ovarian follicular hormone daily. At the end of that time no menstrual periods had occurred and there was no change in body weight. From February 1 to February 7 she had severe abdominal cramps. These disappeared and did not recur. During the month of March 4000 units of the hormone were administered. No demonstrable change occurred. On May 1 physical examination revealed essentially the same findings as on admission. There was no change in body weight or height.

A reply to a follow-up letter was received on December 10, 1931. The patient's mother stated that the girl had had no menstrual bleeding and that there had been no change in her condition except a slight gain in body weight.

Result. No effect was noted after the administration of approximately 7000 units of the ovarian follicular hormone in a girl of 16 years, who showed the physical characteristics usually interpreted as being due to anterior pituitary ovarian disturbances. The amenorrhea persisted.

CASE 7.—E. S. (Cornell Clinic, A69382), Jewish female, married, aged 36 years, was admitted to experimental group on December 9, complaining of lack of menstruation. Patient had always been healthy. Two scanty

menstrual periods had occurred at the age of 15 years. There had been none since then. She had been married for the past 5 years and no pregnancies had occurred. Her husband had been shown to have active spermatozoa.

Physical examination showed a healthy looking woman. Weight, 138 pounds. There was increased hair growth of the face and legs and the abdominal distribution of hair was of the masculine variety. The hands and feet were large. The uterus and cervix were small and of the infantile type. The diagnosis was amenorrhea of anterior pituitary ovarian type.

Treatment. Between December 9 and March 9 the patient used 4000 Allen-Doisy units of the follicular hormone. No menstrual bleeding or abdominal cramps occurred. There was no change in body weight.

Result. Four thousand units of the hormone distributed over a 3 months' time period produced no effect in a women, aged 36 years, with anterior pituitary ovarian dysfunction.

Dicussion. Strikingly beneficial results were obtained in 3 of the 8 cases of natural menopause treated with ovarian follicular hormone. In each of these 3 instances the menopause was of less than 1 year's duration. In these cases there was marked relief of symptoms and reëstablishment of uterine bleeding. It is fully realized that there is no particular benefit to be gained by reëstablishing uterine bleeding after the menopause has set in. In the present experiment it was simply regarded as evidence that the hormone was physiologically active and capable of producing an effect which could not be considered psychic in these cases. All 3 of these individuals showed partial loss of excess weight. In 3 of the 5 cases in which the menopause was of 2 to 5 years' duration, there was considerable symptomatic relief but no return of menstrual bleeding after treatment. These results were classified as "fair," since it is recognized that any form of therapy, and especially the so-called "glandular therapy," can have a striking psychic effect on this type of case. There did appear, however, to be considerable relief from the "hot flushes" in these individuals. These had been a most distressing symptom in all of the cases. A variable length of time after treatment was begun the patients noted a definite diminution in the frequency and duration of the flushes. In 3 cases they stopped occurring. In 1 instance, however, even after several thousand units of the hormone, there was no symptomatic relief.

The 2 cases of artificial menopause both obtained what appeared to be remarkable relief from headaches, hot flushes and nervousness. In both instances this result did not manifest itself until nearly 1000 units had been used. The relief continued for approximately 1 week after therapy was stopped during a control period. At the end of that time the symptoms returned and persisted until the hormone was again started. In 1 individual, marked congestion of the breasts was noted after using relatively large quantities of the hormone. These 2 cases of artificial menopause could be maintained symptom free on approximately 500 units of the hormone each per month. No definite effect on the blood pressure was noted

in any of the cases during the period of hormone administration. There was a loss of 10 pounds or more in weight, in the course of the 3 months' duration of the experiment, in 6 of the 10 cases.

The cases of amenorrhea which were regarded as being due to simple follicle hormone insufficiency responded well to substitution therapy. Cases 4 and 5 have been selected as typical examples of this group. In striking contrast are Cases 6 and 7, in which no response occurred in spite of the administration of several thousand units of the hormone. These 2 latter cases exemplify a group which is usually regarded as being due primarily to anterior pituitary dyscrasia. Their lack of response to the follicle hormone confirms this classification.

Conclusion. A series of 20 cases is presented in which the intravaginal administration of the ovarian follicle hormone has been alternated with control periods. It would appear that the preparation of the hormone used was physiologically active in humans, as evidenced by the induction of uterine bleeding. Further, data are presented which suggest that this hormone of the ovarian follicle is of definite clinical therapeutic value in the treatment of the disagreeable symptoms which may accompany the menopause and of the amenorrhea due to an insufficiency of that hormone. No beneficial results were obtained when the hormone was administered to cases of amenorrhea which showed clinical evidences of an anterior pituitary etiology.

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HYPERPERISTALTIC ELECTROGRAPHIC EFFECTS.*

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The usefulness of the electrocardiogram in the diagnosis of conduction disturbances of the heart by portraying the nature, direction, sequence and timing of the cardiac stimulation suggests the application of the electrocardiographic method to the other common type of rhythmic activity represented by gastrointestinal peristalsis. The basis of both manifestations is the action current incident to the muscle contraction. Direct electrogastrography has been performed by Alvarez[1] and Alvarez and Mahoney[2] in cats by the use of a modified d'Arsonval galvanometer and small calomel electrodes made up with Locke's solution clamped against the bowel wall with small wooden clamps. Simultaneous mechanograms corresponded with the electrograms. In 1922 Alvarez[3] succeeded in obtaining a record in the human by placing electrodes directly on the abdominal wall of an emaciated old woman with visible peristalsis. He failed to duplicate these findings in better muscled subjects.

The Present Problem. It had long been considered that the visible peristalsis accompanying congenital hypertrophic pyloric stenosis offered a favorable opportunity for electrographic registration because such vigorous muscle contraction must necessarily develop strong action currents and positive results could be checked visually. Opposed to this idea, the impression has been current that the peristaltic action current is too slow to be recorded by the ordinary string galvanometer.

In the first attempts to obtain electrograms of gastric peristalsis mesh electrodes fitting the curvature of the baby's abdomen were applied in the regions corresponding to the fundic and pyloric portions of the stomach. The ordinary Hindle galvanometer was used, and a preliminary announcement was made in 1926.[4] Objections may be offered to direct abdominal leads on account of the possible artefacts produced by mechanical shifts in the position of the electrodes, a distortion aggravated by respiratory movements. Subsequently, the indirect or ordinary electrocardiographic leads

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were employed because this procedure would avoid the objections to the direct leads and because the former would afford a norm, deviations from which associated with visible peristaltic waves might justly be ascribed to these contractions. In other words it was presumed that hyperperistalsis like skeletal muscle contraction would develop sufficient action current to interfere with or alter the known constant, viz., electrocardiogram. Furthermore, indirect leads enjoy the advantage of ease of application. It is more practicable to keep the baby quiet with electrodes attached to the extremities, and records merely require patience to achieve a state of quiet in the child. Lead III was arbitrarily chosen and was continued throughout the observations because it yielded positive results at once.

Records were obtained from 2 infants with congenital hypertrophic pyloric stenosis presenting readily visible gastric peristalsis. Intestinal peristalsis was recorded in an infant with congenital hypertrophic dilatation of the colon (Hirschsprung's disease) whose peristaltic waves rushed over the abdomen in different directions simultaneously. In the course of this tracing an unexpected curve appeared without visible peristalsis or other movement of the child. Upon investigation it was found that the infant had extruded a stool, by rectal peristalsis apparently. Finally, in connection with intestinal peristalsis an unusual record will be introduced: it was obtained in the course of a routine electrocardiographic examination of a patient with audible peristaltic rumblings.

Gastric Hyperperistalsis. CASE 1.—R. F., aged 5 weeks, male, first born, birth weight 7 pounds 7 ounces, was admitted to the Sarah Morris Hospital, March 30, 1931, weighing 8 pounds. He had been under observation since the age of 2 weeks when symptoms of stenosis first became evident. On admission, the typical picture presented consisting of projectile vomiting following ingestions of feedings and water, scanty stools, scanty urine, stationary weight terminating in loss, visible gastric peristalsis and tumor palpable to the right of the umbilicus. The diagnosis of obstruction was confirmed by radiological examination, and surgical exposure revealed a large hypertrophic pyloric tumor. The electrogram was obtained preceding operation.

Comment. The alteration of the normal level base line of the electrocardiogram manifested by a wavelike shift occurs simultaneous with the peristaltic wave. More specifically, the noticeable change occurred when the visible wave approached the midline of the abdomen in its right-sided progress. It was our practice to notify the technician at the outset of the peristaltic bulge in the left hypochondrium, but she reported no marked deviation of the string until we found the wave had reached the midarea. When the procedure was reversed the technician invariably reported the change in the string when the observer noted the wave well advanced to the midline. This observation confirms the findings of Alvarez. In his experiments on the exposed stomach the wave seemed to arise about

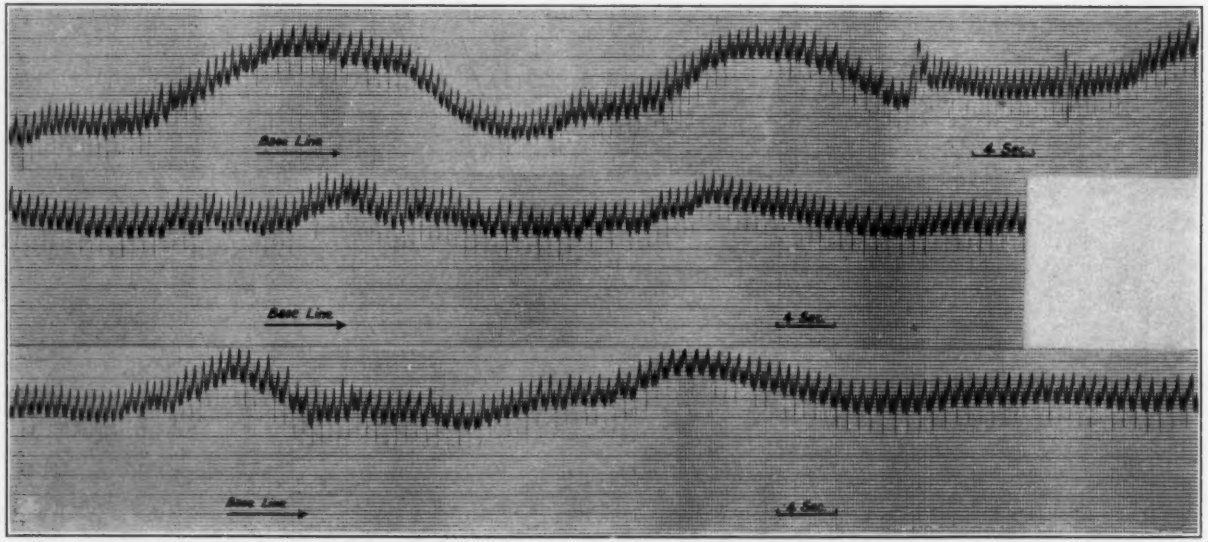

FIG. 1.—Gastric hyperperistaltic effects from a case of congenital hypertrophic pyloric stenosis. In this and the following figures, the electrocardiograms occur as usual. The peristaltic effects are represented by excusions from the base line. Note the camera is slowed to $\frac{1}{8}$ of the normal rate. The normal rate was used in Figs. 2 and 3, the earlier records.

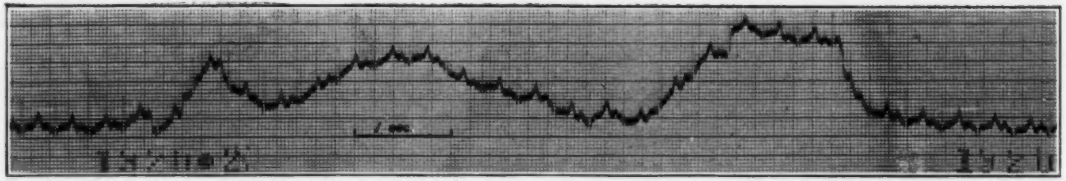

FIG. 2.—Intestinal hyperperistaltic effects from a case of congenital hypertrophic dilatation of the colon (Hirschsprung's disease).

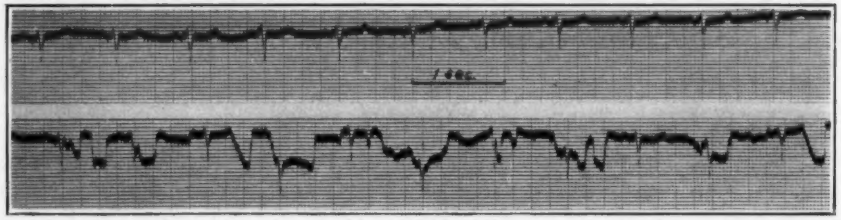

FIG. 3.—Borborygmic effects (irregular and arrhythmic) obtained during the routine electrocardiographic examination of a patient with cardiac symptoms. The upper strip was obtained during quiescence. The lower strip was recorded during the same session coincident with active, audible peristaltic rumblings.

the middle of the stomach. The lag in the electrographic record may be explained on the basis of the summation of current which manifests itself maximally or optimally with regard to the cardiac current at the mid-position of the peristaltic wave. The peristaltic disturbance as evidenced by the curves in the electrocardiographic base line occurs at the rate of three per minute, a duration of 20 seconds. This agrees with the frequency of gastric peristaltic action as judged by the rise in intragastric pressure determined by the balloon method[5] and likewise found by Alvarez.

Intestinal Hyperperistalsis. CASE 2.—N. S., aged 3 years, female, was admitted to the Post Graduate Hospital, October 17, 1924 for feeding difficulty and retarded development since birth and abdominal distention particularly conspicuous for the past year. Briefly, the child presented an emaciation characteristic of a dystrophy of long standing, and her color was sallow. The abdomen was greatly distended, sometimes hard and at other times quite soft. The coils of colon and their large peristaltic undulations passing under the abdominal wall were very striking. The tongue was the geographical type, and there were marked teeth grinding and finger movements. Radiographic examination by the opaque enema disclosed "a very much enlarged colon with not only a very great increase in circumference but also a marked redundancy in the length of the sigmoid loop which presented high up on the right side in the usual position of the cecum." The electrographic record was obtained November 24, 1924. Subsequently, a sigmoidectomy was performed with an end-to-end anastomosis. Death followed, and necropsy disclosed peritonitis.

Comment. This record reproduces frequent and irregularly timed changes in the base line occurring when the meandering colonic peristalsis resulted in currents physiologically adequate to interfere with the cardiac picture. The frequency and irregularity of interval and excursion in the intestinal type of peristalsis was predictable because these waves do not traverse a definite path across the abdomen like gastric waves. The hyperperistalsis in Hirschsprung's disease occurs commonly in several segments simultaneously and is due to the functional if not anatomical obstruction characteristic of this condition. Prominent as the frequency and irregularity appear in the record submitted, these factors are nevertheless minimized in comparison with the preceding gastric tracing because the latter was taken at less than one-sixth of the speed of the former. The intestinal record taken early in our observations was obtained without altering the speed of the regular cardiographic camera. Consequently, the breadth of the response is emphasized with reciprocal lessening of the base-line excursion in comparison with the picture reproduced by a slower camera. At the rate of the gastric curve, the intestinal record should be imagined one-sixth its length.

During the record a single wave occurred without visible accompaniment. Olfactory evidence testified to the passing of a stool readily confirmed by inspection. It is likely that the invisible rectal peristalsis was recorded as a single wave due to a single course of action current resembling the picture of gastric peristalsis.

CASE 3.—I. G., aged 54 years, was referred from the Mandel Clinic to the Heart Station for electrocardiographic examination on the basis of a history of dyspnea on exertion, hypertension, and seizures of angina pectoris. The records presented were obtained May 28, 1930. Three months later the patient was hospitalized for coronary disease. Death occurred September 17, 1930. No necropsy.

Comment. The circumstances attending the inclusion of this record are noteworthy. The bizarre electrographic records obtained in infants manifesting hyperperistalsis recalled to the technician the peculiar record obtained in a patient almost a year previously. During the course of a routine cardiogram she observed strange movements of the string. Leaving her recording room, she approached the patient to note and inquire whether an artefact had been produced. The patient was lying perfectly quiet, but she was struck by the sound of loud borborygmi emanating from him. She continued to take a strip of record during this period. It is a coincidence that Lead III which was used in our deliberate efforts, was connected at this time. The upper strip illustrated was obtained during a quiet period although there seems to be a slow shift in the base line even here. This was more conspicuous in Lead II (not reproduced). The lower strip was taken during the active, audible peristaltic rumblings. The interpretation of this record is peculiarly significant:

"May 28, 1930. Sinus arrhythmia. Rate average 82. *P–R* interval 0.14 seconds. *R* is slurred in Leads I and II and notched in Lead III. Left axis deviation. No evidence of myocardial abnormality other than left ventricular preponderance. (The other part of Lead III was taken during audible peristaltic rumblings. The ventricular complexes are unchanged. The rest of the bizarre tracing cannot be interpreted. Record of peristaltic wave?)"*

On two subsequent occasions this patient was examined with no reappearance of the "bizarre" finding. The electrocardiograms on these occasions resembled the previous typically cardiac record. The peculiar effect observed in this condition is likewise probably due to vigorous intestinal peristalsis, sufficiently active to produce loud borborygmi. It is presented as it stands as an unusual electrographic effect accompanying intestinal hyperperistalsis in the absence of other evident cause and resembling by its irregularity the effect produced by the other type of intestinal hyperperistalsis found in Hirschsprung's disease. The more rapid base line undulations in this record as compared with Fig. 2 may be explained on the basis of summations of distant synchronous peristaltic activity

* Since there was no clue to the tracing except that a notation of the rumbling in explanation of the curious curve had been appended to the diagnostic card and a strip of tracing had been preserved, it was necessary to search systematically through the records of the department to secure the data. About 6500 cards were examined before finding the record. In the meantime several thousand films had likewise been subjected to scrutiny. This yielded many records with suggestively shifting base lines.

due both to the larger size of the individual and the wider distribution of the activity.

Discussion. All results were obtained while the subject was quiet or asleep to avoid artefacts due to contraction of skeletal muscles. This proved easy in the child with Hirschsprung's disease. Many attempts in infants with pyloric stensosis failed because these babies are irritable unless markedly atrophic. The fretfulness is provokingly aggravated at the height of the peristaltic wave due to the pain or pressure. This has been noted by the author and others during observations on hunger contractions in infancy.[6] Frequently, a spasm manifests itself in the facial expression of the infant asleep during the experiment. Sedatives were not used in this series to obviate objections to the results. However, sedatives not markedly affecting peristalsis should greatly facilitate observations of this kind. In this connection, an attempt to obtain a record during light ether anesthesia immediately preliminary to surgical correction in the operating theater proved a failure as predictable.

It is not claimed that the waves recorded are true reproductions of peristaltic waves. It should be appreciated that the electrocardiogram is not the record of individual impulses but represents merely the moving picture of the changing algebraic sums of innumerable action currents in innumerable anatomic portions of the heart running in different directions simultaneously.[7] Similarly, the peristaltic "effect" is an electrogastrogram or an electroenterogram depending on the organ of origin and is merely the algebraic summation of innumerable action currents produced in a relatively long, more or less hollow viscus manifesting contraction waves preceded by inhibition waves and constantly changing its position.

Indirect and direct considerations testify to the authenticity of electrographic registration of peristaltic effects. From the indirect standpoint it is obvious from a study of the tracings submitted that these changes differ from artefacts due to skeletal muscle contraction and from respiratory interference. From the direct standpoint there is coincident visual evidence of unusually strong smooth muscle contraction. Furthermore, the result of gastric peristalsis is a rather regular wave to be expected in a movement following a definite direction, and its duration coincides with the time determined by mechanical methods of examination. Regularity in the intestinal record is lacking, likewise to be expected, because the anatomic distribution of the intestinal coil is irregular. Most gratifying to the confirmation of the above is the gratuitous check offered these findings by the unpremeditated and unprejudiced record of the patient with borborygmi.

It follows logically that peristaltic effects must manifest themselves as supposed artefacts in the countless records already gathered, but there is no reference to such effects. In a review of 15,600

records, Esler and White[8] divide the artefacts into extrinsic and intrinsic depending on whether the cause lies within or without the subject. Smooth muscle effects or artefacts are not mentioned in their catalogue, but they conclude that the frequent electrical distortions demand more consideration than is usually accorded them. Shifts in the base line are frequently seen in electrocardiograms. Wenckebach and Winterberg[9] published several electrograms presenting significant shifts incidental to a study of the effect of vagus pressure and other measures. It is conceivable that the base line shifts are due to peristalsis which vagus stimulation, at least, may produce. Furthermore, in the search through our files for the electrocardiogram presented in Fig. 3 many films were found with varying degrees of base line shifts. It is possible that some of these were peristaltic effects.

It is a curious commentary that although this study was undertaken to obtain electroperistaltograms, particularly electrogastrograms, it has resolved itself, in fact, to an elucidation of an electrographic effect due to hyperperistalsis.

Summary. An indirect electrographic record of gastric hyperperistalsis is presented.

The electrogram resembles the mechanogram in form and frequency.

Indirect electrographic records of intestinal hyperperistalsis are submitted from three types of intestinal activity.

The peristaltic effect on the electrocardiogram was predictable by nature of its contractile genesis.

It may be assumed that these effects have been previously recorded but have remained overlooked or misunderstood, since there is no previous record of this observation.

Further study should reveal a new field of fact in electrographic effects and peristaltic activity.

NOTE.—Acknowledgment is made of the valuable suggestions and criticism rendered by Dr. Louis N. Katz, Physiologist and Director of Cardiovascular Research, Michael Reese Hospital.

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PELLAGRA: IMPROVEMENT WHILE TAKING SO-CALLED "PELLAGRA-PRODUCING" DIET.

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For decades investigators have sought the cause of pellagra and to this date uniform agreement as to the etiologic factor is lacking.[1,2,3] Important evidence has accumulated which suggests a deficiency in diet as a cause. Some investigators believe that the production of the clinical disease depends on a deficient diet plus some additional factor, perhaps infection.[1] It is of interest that the relationship of a poor diet to pellagra has been stressed since its earliest recognition. Goldberger and his coworkers[3,4,5,6,7] have brought forward considerable evidence toward establishing pellagra as a dietary deficiency disease. They have described the production and the cure of pellagra in human beings by a means of dietary manipulation. They particularly associate the condition with lack of vitamin G (B_2). It seems fair to state that current opinion favors a dietary explanation of the disease.

The majority of the cases of pellagra observed in the northern part of the United States are associated with chronic alcoholic intoxication. The nature of the relationship of alcohol to the development of the disease is a moot question. It is certain that pellagra occurs in people who do not drink. In some instances a relationship between alcoholic debauches and the development of the disease seems assured. The majority of workers feel that repeated indulgence in alcohol at times prevents an adequate food intake, thus favoring the production of pellagra. Regardless of the difference of opinion concerning the relationship of true pellagra to postalcoholic dermatitis, the lesions in the two conditions appear identical.

Many drugs, minerals and diets have been proposed as a cure for this disease. Inevitable controversy has arisen as to their efficacy. Since pellagra is such a variable disease, it seemed especially worthwhile to study the acute phases under strict experimental conditions.

The present report deals with the study of 6 cases of pellagra and their response to a diet low in minerals and in vitamins C, D and G.

Materials and Methods. The 6 cases chosen for this experiment were typical. Four of the patients were white males and the other 2 were negresses. All had a definite history of a low food intake, and 3 of the males and 1 of the females had a history of alcoholism.

Five of the patients had stomatitis, 4 patients had diarrhea and anal lesions and 4 had mild mental symptoms. Bilaterally symmetric dermatitis characteristic of pellagra was found on the hands of all patients. Both females had vaginal ulcerations and large butterfly-shaped, symmetric lesions of the vulva, thighs and anus, typical of pellagra. The reflexes were essentially normal in all patients.

Each patient received a daily diet of 2300 calories (carbohydrate, 1700; protein, 110; fat, 490) consisting of cornmeal mush, cornmeal muffins, pork fat, maple syrup, polished rice, cornstarch pudding, coffee and sugar. This diet was administered from the time the patient entered the hospital until the skin lesions had cleared with the exception of Case 5 (see case history). Every effort was made to induce the patients to eat the full 2300 calories. They were carefully watched and were not allowed any other nourishment.

The diet used in this experiment seems even more restricted in mineral content and in vitamins D, C and G than Goldberger's pellagra-producing diet.[7] The present diet does not contain the following foods that are found in Goldberger's pellagra-producing diet—cabbage, collards, turnips, sweet potatoes, wheat flour and hominy grits. (He produced pellagrous lesions of the scrotum in 6 of 11 normal subjects after 6 months on his diet.) While the diet used in this experiment is restricted in vitamins D, C and G, it is not believed that all the traces of the vitamins are absent. It is noteworthy that the vitamins and protein content of this diet are less adequate for normal nutrition than Goldberger's diet.

The case histories follow in the order observed in the hospital:

CASE 1.—G. H. (No. 134043), a white male, aged 48 years, entered the hospital complaining of burning, itching and swelling of the hands of 10 days' duration.

Family history and *past history* were irrelevant.

Present Illness. Patient enjoyed good health until 8 months before admission. At that time he became depressed, began drinking wood alcohol, and rarely ate any food, resulting in a loss of 30 pounds in weight. Three weeks prior to admission (October 21, 1930) to the hospital he observed marked soreness and burning of the tongue and a severe diarrhea, 8 to 12 stools a day. Ten days later he developed large, symmetrical red areas over the dorsum of his hands which soon become swollen. They were pruritic and a yellowish material oozed from their surfaces. At this time he noticed vesicles over his lips and the pain in his tongue increased. He had no symptoms of dementia.

Physical Examination. Showed a somewhat undernourished white male, aged 48 years, mentally clear, lying quietly in bed. The dorsum of both hands and wrists were covered by large, symmetrical areas of reddish color. They were sharply defined from the surrounding skin. The epithelium over the lesions was tense and in areas replaced by large cracks. Small vesicles and large areas of crust formation were observed. The general physical examination was negative.

Laboratory Findings. Red blood cells, 4,900,000; hemoglobin, 75 per cent. Gastric analysis showed an absence of free hydrochloric acid after alcohol administration, but a trace was found after histamin injection.

Progress. Patient was placed on the experimental diet. The diarrhea ceased on the second day and on the fourth day his mouth and tongue were free of symptoms. Desquamation of the skin lesions was observed on the fifth day and was complete on the twelfth day. All signs and symptoms disappeared during the first 2 weeks. He gained 3 pounds in weight and was discharged on the twenty-third hospital day. He appeared well when seen 2 weeks later, despite several mild alcoholic debauches in the interval.

CASE 2.—E. F. (No. 123692), a divorced negress, aged 41 years, entered the hospital complaining of a vaginal discharge of several weeks' duration.

Family history and *past history* were irrelevant.

Present Illness. For several years the patient had lead a solitary life, prepared her own food and subsisted largely on oatmeal. She does not know whether or not she has lost any weight. About 6 months before admission she observed hyperpigmentation of the skin around the vagina and rectum and over the dorsum of the hands. Her condition remained about the same until 3 weeks prior to her hospital entry, when all lesions rapidly became worse and she observed a foul-smelling watery discharge from the vagina. At about this time she developed a severe diarrhea, 15 to 20 stools a day. The symptoms remained constant until her arrival at the hospital (February 13, 1931).

Physical Examination. Showed a well-developed but edematous negress, aged 41 years, lying placidly in bed. She was moderately demented. The eyelids, face, extremities and abdominal wall were edematous. The skin over the hands, wrists and adjacent portions of the arms was thickened, rough and pigmented. These lesions were bilaterally symmetrical. Her neck was similarly involved. A large symmetrically placed area involved the vulva and adjacent portions of the thighs and anus. It was pigmented, thickened and undergoing maceration. The tongue and pharyngeal walls were reddened and swollen. Mucous membranes of the mouth and vagina were bright red in color. Patient had classical physical signs of mitral stenosis associated with cardiac decompensation.

Laboratory Findings. Red blood cells, 4,300,000; hemoglobin, 75 per cent. Repeated smears from the cervix showed many inflammatory cells and almost pure infection by spirochetes. Free hydrochloric acid was absent from the gastric contents after alcohol and histamin administrations.

Progress. The skin lesions began to desquamate during the latter part of the second week on the experimental diet. This process slowly progressed and by the end of the fifth week the epithelium was thin, smooth and shiny. It still remained deeply pigmented. Mucous membranes of the mouth and vagina slowly improved and appeared normal during the fifth week. Patient remained 8 weeks on this diet. Her appetite became poor toward the latter part of the experiment, perhaps due to the vitamin C deficiency, and she ate only when urged. When seen 2 months after her discharge from the hospital she was decompensated, and the sites of the former pellagrous lesions were covered by thin, atrophic, deeply pigmented epithelium. The mouth and vagina appeared normal. The dementia was unchanged.

CASE 3.—T. S. (No. 141315), a white male, aged 44 years, entered the hospital complaining of itching of the hands of 3 weeks' duration.

Family history and *past history* were irrelevant.

Present Illness. During the spring of each of the past 4 years the patient had areas of itching and burning, symmetrically placed over the dorsum of the hands and wrists, followed by a dermatitis, which each time appeared only after weeks of drinking. With the onset of the skin lesions he ceased drinking, and his hands returned to normal several weeks later.

During the 8 months preceding his entrance to the hospital he drank

FIG. 1.—Showing the symmetrical lesions of pellagra.

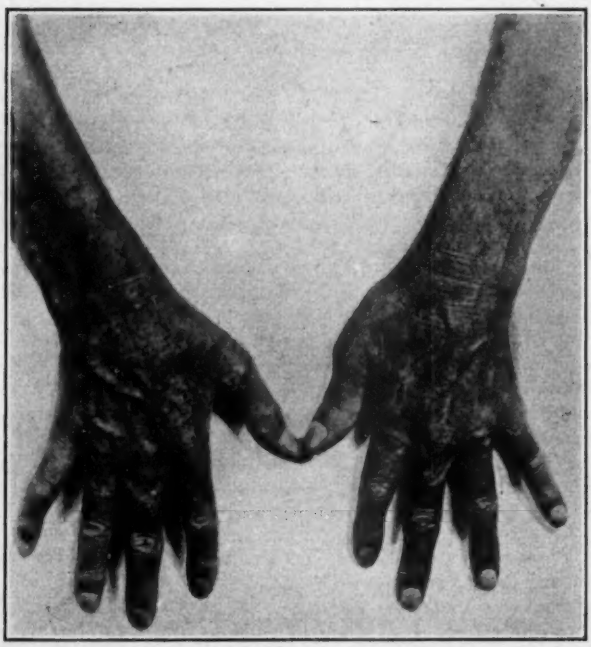

FIG. 2.—The same hands 23 days later. Note the chief residual change is due to freckles.

over 1 pint of denatured alcohol daily and rarely ate food. He lost 20 pounds in weight. Three weeks before entrance (July 7, 1931) he observed large areas of redness over the dorsum of the hands. A week later he noticed a band of similar appearance surrounding his neck. Soon afterward vesicles appeared along the neck and hands. A few days later each of the lesions became pruritic. At about this time the stools became numerous and watery in character. Several days before coming to the hospital he observed pitting edema of the ankles and numbness and burning of the hands and feet.

Physical Examination. Showed a fairly well-nourished, middle-aged man, mentally clear, lying quietly in bed. The tongue was beefy red and swollen. The pharyngeal walls and mucous membranes were reddened. Extending around his neck was an area, several centimeters in width, which consisted of large crusts surrounded by serohemorrhagic exudate. The dorsum of the hands and the adjacent portions of the arms were covered by bilaterally symmetrical lesions characteristic of pellagra. They were raised and well demarcated from the adjoining skin and contained innumerable vesicles, crusts and areas of hemorrhage. Smaller but similar appearing symmetrical areas were observed on the dorsum of both great toes. Pitting edema of the ankles and hyperesthesia of the feet were demonstrated. The reflexes were normal.

Laboratory Findings. Red blood cells, on admission, 2,750,000; hemoglobin, 35 per cent. Red blood cells, at discharge, 3,910,000; hemoglobin, 70 per cent. Free hydrochloric acid was absent after the administration of histamin.

Progress. Patient was given the experimental diet and the lesions improved considerably during the first week. During the second week the dermatitis and the redness of the mucous membranes, tongue and pharynx disappeared. The patient lost 17 pounds while in the hospital, some of which was undoubtedly associated with the disappearance of the edema. He was discharged after 37 days on the diet. He was seen 6 days later and was in good health.

Case 4.—R. K. (No. 135450), a white male, aged 73 years, entered the hospital complaining of painful, burning areas on the hands.

Family history and *past history* were irrelevant.

Present Illness. Patient had been in the habit of drinking 1 pint a day or more of wine for many months. For an unknown period of time he had had a poor appetite and lived on occasional small amounts of coffee, bread, potatoes and meat. During this time he lost 10 pounds in weight. He stated that the pruritic lesions appeared on the dorsum of the hands 6 days prior to admission (July 28, 1931). The following day these areas were observed to contain vesicles and blood oozed from some of the cracks. He had a mild coryza several days before entering the hospital. There was no history of diarrhea.

Physical Examination. Revealed a well-developed and nourished elderly man, lying quietly in bed. He had a moderate amount of dementia (it is possible cerebral sclerosis may have been the etiologic factor). The pharyngeal wall and the tip of the tongue were reddened. Over the dorsum of the lower third of both forearms and extending over the hands and fingers were symmetrical, well-demarcated lesions characteristic of pellagra. Vesicles and crusts were observed. The palpable arteries were hard and tortuous.

Laboratory Findings. Red blood cells, 3,730,000; hemoglobin, 79 per cent. Free hydrochloric acid was absent from the gastric content after administration of alcohol and histamin.

Progress. On admission the patient had an unexplained temperature of 39° C. which fell to normal within a few days. He was given the experi-

mental diet and there was rapid improvement of the skin lesions. He remained on the diet 20 days and lost 15 pounds. He was discharged improved. When seen 2 weeks later he was in good condition.

Case 5.—A. S. (No. 135696), a married negress, aged 25 years, entered the hospital complaining of discoloration of the hands and feet, and pain in the hands, feet, mouth, rectum and vulva of more than 3 months' duration.

Family history and *past history* were irrelevant.

Present Illness. Patient had drunk heavily of strong liquor each day for 2 years. During the past year she ate occasional small amounts of green vegetables, fruits, cereals and meat. About 3 months before admission to the hospital (July 1, 1930) she noticed soreness of the throat, rectum, vagina and increased pain and pigmentation in her hands and feet. From that time on she lost weight constantly, and though her pains were less severe, her lesions became worse. Diarrhea and dermatitis were not present.

Physical Examination. Showed a well-developed, undernourished negress, lying comfortably in bed. The tongue, throat and mucous membranes were diffusely reddened. Symmetrical glovelike lesions extended over the hands and arms. The vagina and cervix were inflamed and there were small symmetrical areas of inflammation around the anus.

Laboratory Findings. Gastric analysis showed no free hydrochloric acid after alcohol administration but a trace of free acid was demonstrated after histamin injection.

Progress. Patient was given a high caloric diet and frequent large feedings of tomato juice and yeast. Dermatitis slowly improved. She was discharged 51 days after admission.

The patient was readmitted to the hospital 13 months later with symptoms as before.

Interval Note. For several months after her discharge the patient continued to improve but then again started to drink heavily, averaging from ½ to 1 pint of whisky and several bottles of beer daily. Her daily diet often consisted of "a bit of vegetable, a swallow of milk or a morsel of salt pork." Lesions similar to those of the first admission developed at least 6 months prior to readmission. In addition, she had large areas of pruritus and discoloration about the vagina and elbows. For the next few months her mouth and throat became alternately sore and well. The month preceding readmission her sore throat returned, leukorrheal discharge became marked and she experienced dribbling and burning on urination. During the 2 weeks preceding admission she became worse, vomited often and lost 10 pounds in weight.

Physical Examination. Showed a well-developed, undernourished negress, aged 25 years, lying in bed. The throat, right side of the mouth, sides and tip of the tongue were injected. Large bilaterally symmetrical areas of thickened and pigmented epithelium were located over the hands, wrists, elbows, antecubital fossæ and perineal areas. The pigmented and thickened epithelium around the vagina and anus was macerated. The perineal lesion measured 16 cm. across.

Laboratory Findings. Red blood cells, 3,340,000; hemoglobin, 60 per cent. Gastric analysis on admission showed an absence of free hydrochloric acid after the administration of alcohol and histamin. Two weeks later a trace of hydrochloric acid was demonstrated following histamin injection.

Progress. Patient was placed on the experimental diet which was well tolerated for 2 weeks. During this time she gained 5 pounds in weight, and the dermatitis improved somewhat but the soreness of the mouth and throat became worse. Patient received disturbing news from her mother

and refused to eat. During the next 3½ days she ate less than 500 calories, and her diet was changed to include anything that she might wish to eat. She then proceeded to vomit everything she ingested during the next 5½ days. The lesions progressed rapidly and she lost 12 pounds in weight. A duodenal tube was inserted and she was fed a high caloric diet rich in vitamins and proteins. She gradually improved and the remainder of her convalescence was uneventful. She was seen 2 months later and the sites of the pellagrous lesions were covered by thin, deeply pigmented epithelium.

It is noteworthy that while the full number of calories of the experimental diet were ingested, the skin lesions improved slowly; but when the patient refused to eat the lesions rapidly became worse.

CASE 6.—C. C. (No. 142953), a Norwegian-born laborer, aged 53 years, entered the hospital because of painful lesions of the hands, neck and face of 6 weeks' duration.

Family history and *past history* irrelevant.

Present Illness. For the past 4 or 5 months the patient has been forced, by economic reasons, to limit his diet to bread, coffee and an occasional piece of meat. Six weeks prior to entry the patient observed symmetrical lesions of redness over the dorsum of the hands, followed soon afterward by a similar process on the neck and face. The lesions on the hands gradually involved the phalanges and lower two-thirds of the arms. He has had diarrhea and some loss of memory for an indefinite time. For several weeks he has had a mild cold. During the past year he has lost 50 pounds in weight. The patient has not imbibed any alcoholic beverages for 20 years.

Physical Examination. Showed a well-developed, emaciated white man, lying quietly in bed. Bilaterally symmetrical areas of dermatitis extended over the fingers, hands and arms. Encircling the neck and over the face and nose were large similar appearing, reddish areas with vesicle formation and crusting. The pharyngeal walls were injected. The tongue was smooth and over its right side was an area of redness, 0.5 cm. across. The remainder of the physical examination was negative.

Laboratory Findings. Red blood cells, 4,430,000; hemoglobin, 80 per cent. Gastric analysis showed no free hydrochloric acid after alcohol or histamin administration.

Progress. The patient was placed on the experimental diet and the skin lesions rapidly became better. They were replaced by thin, pink colored normal skin at the end of 12 days. The red area described on the side of the tongue slowly spread over the surface of the entire organ. It was never associated with burning or pain. The diarrhea became somewhat better. The sensorium cleared, but the weight remained constant at 101 pounds. Because of extreme emaciation and the fear of the development of another disease, he was placed on a high caloric diet at the end of 3 weeks. The tongue rapidly returned to normal and his weight gradually rose to 110 pounds. He was seen 2 months after discharge and was in good health.

Discussion. It has been shown in the experiments reported here that the skin lesions of 5 pellagrins improved strikingly on a diet low in vitamins C, D and G (pellagra-preventive factor). The other case (Case 5) in the series had partial improvement of the dermatitis, a gain of 5 pounds in weight, and a return of gastric acidity during the 3 weeks she tolerated the diet. However, during these 3 weeks on the restricted diet her stomatitis slowly became worse. She became mentally upset and refused food. The diet

was changed and tube feeding was undertaken, with recovery of the patient. It is worthy of emphasis that her lesions became worse during the 9 days that her caloric intake was so low. As soon as the skin lesions cleared several of these patients were removed from this experimental diet in order that they might not fall victim to some other diseases. Some were greatly emaciated and further experimentation might have proved dangerous. Four of the patients suffered a loss of weight. This is partially explained by the disappearance of edema in 3 cases.

In general, the skin lesions improved during the first or second hospital week and the epithelium was apparently recovered by the third week. Many of the common symptoms were relieved while the patient was on this diet, though dementia and burning of the feet did not improve.

The interpretation of the striking improvement in the dermatitis is difficult. When first seen some of these patients had temporary mild infection and in all instances the patients were given rest, thus making it difficult to say that all of the improvement was due to the diet. It is perhaps possible that these patients were on the road to recovery and continued to improve despite the restriction of diet. Their clinical histories indicate that they had eaten little prior to their admission to the hospital and in all cases the patients stated they were becoming worse when they sought relief in the hospital. While this diet is woefully deficient in many respects, it is not thought to be devoid of all traces of vitamins. Perhaps the patients received more essential elements from this restricted diet than from the paucity of food they ingested before coming to the hospital. The observations that Case 5 rapidly became worse when she refused the diet is suggestive that this diet is certainly more beneficial than the absence of food. Of course, the question as to the degree of depletion of the various substances in the bodies of these patients at the time they came to the hospital must remain unanswered. It seems logical that if pellagra is caused by specific depletion of some factor, this factor would be low at the time of the disease.

It is impossible to know whether or not the skin lesions would have recurred had the patient continued indefinitely on this diet. At the present time it seems logical to think of a secondary factor in the development of pellagra. For example, we observed a case who developed pellagra in her home despite the fact that she ate generously of the usual household foods and did not take alcoholic beverages. When first seen in the hospital this patient was regarded as being an unusually severe case and was not placed on the experimental diet. She died 5 days after admission to the hospital despite the fact that she was getting a generous diet high in proteins and the known vitamins. The postmortem examination

revealed no adequate cause for her death. In view of Castle's[8] recent work, it seems that there may be an underlying gastric disorder. This theory is supported by the observation that a fairly high percentage of the cases have achlorhydria which usually disappears several months after recovery from the disease. On the other hand, I have demonstrated[9] that ventriculin, which is curative for pernicious anemia, protects and cures the pellagra-like condition described in rats. This observation suggests some etiological relationship between vitamin G deficiency and the development of pernicious anemia.

The diet given the pellagrins in this experiment has been demonstrated to be inadequate for the proper nutrition of young rats.[9] When limited to this diet the rats lost weight, developed alopecia and dermatitis and subsequently died. This fact plus the theoretical dangers of giving a restricted nonpalatable diet to diseased patients make us realize that it should be used with the greatest of care. Although this diet may not be a cure for pellagra, yet these people have improved in spite of it, suggesting that rigidly controlled observations are necessary for further study of this disease.

Summary and Conclusions. 1. It has been shown in the cases reported here that the skin lesions of 5 pellagrins improved strikingly while receiving a diet believed to be lower in protein content and in vitamins C, D and G than so-called pellagra-producing diets.

2. The possibility of a secondary factor in the production of pellagra, perhaps analogous to the gastric defect of pernicious anemia, is thus suggested.

3. The indiscriminate continuous administration of such a restricted diet to pellagrins is not recommended.

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ABSORPTION FROM THE PLEURAL CAVITY OF DOGS.

II. THE LYMPHATIC SYSTEM.*

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IN former communications, the absorptive mechanism from the peritoneal cavity of dogs was described.[2,4] Other studies made on the mechanism of absorption of particulate material from the pleural cavity of dogs have already been published.[3] Part I, the cytologic aspect; Part II, the present study, describes the lymphatic channels of the thorax which appear chiefly responsible for the removal of such particulate matter. The description will be confined to those lymph nodes and vessels that are readily seen by natural methods of filling.

Method of Experiment. A finely divided particulate graphite preparation was injected directly into the pleural space, usually in the ninth interspace. To avoid the parenchyma of the lung manometric readings were first taken, to be sure that the needle was in the pleural cavity, but not in contact with tissue of the lung. The manometer was then detached and a sterile graphite suspension was injected. Ordinarily 5 to 15 cc. was used, the exact amount depending on the weight of the dog. The animals were killed and carefully dissected at intervals following the injection ranging from 1 hour to 4 months. Most of the animals were fed a heavy fat meal approximately 3 hours preceding necropsy to facilitate identification of the cisterna chyli, thoracic duct and related lymph vessels.

Observations. When animals were examined within an hour after the injection of the graphite suspension into the right pleural space, two characteristic observations invariably followed. (1) The injected material acted as an irritant on all the structures within the thorax, causing edema and hyperemia, so that the pleural surfaces were inflamed and edematous and the bloodvessels stood out prominently; (2) the mediastinum was not an impermeable barrier between the two sides of the thorax; in every instance approximately equal amounts of serous effusion were present in both sides of the thorax, regardless of the side into which the graphite had been injected; (3) the inflammatory reaction seemed to grow in intensity up to the eighteenth or twentieth hour; but it

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gradually receded and usually all effusion was absorbed by the fourth or fifth day.

The pleural fluid, as has been described,[4] had certain constant characteristics. It was made up of serum blackened by graphite and contained erythrocytes and leukocytes, as well as phagocytes of the mononuclear variety. In the early experiments, some of the graphite was free within the fluid, but as time progressed and inflammation receded, the amount became reduced until all was included within phagocytes. The earliest phagocytic reaction was demonstrated by the polymorphonuclear leukocytes. Later, there was a gradual increase in the number of nongranular mononuclear phagocytes which we have described as clasmatocytes.

Certain differences in behavior of the serous membranes were uniformly observed. It was significant that the visceral pleura took but small part in the inflammatory reaction. It was never as edematous or hyperemic as the parietal pleura, and although the visceral pleura was literally bathed in black fluid for a period of 4 or 5 days, yet the lymphatic channels of the visceral pleura were never seen and the lymph nodes at the hilum took a lesser part in the absorption than those in other areas, especially the sternal and the tracheal lymph nodes. Nodes of the hilum in this contribution include the bronchopulmonary nodes together with the superior and inferior tracheobronchial group. The gross and the microscopic examination of the lung failed to reveal any evidence that the injected material had passed through the visceral pleura or that the lung contained any of the graphite.

The reaction of the diaphragmatic pleura was essentially similar to that of the pleura covering the lungs. Areas of black coagulum were present here and there, but these were merely adherent and could be brushed off easily. In small isolated areas, however, the granules of graphite were contained in phagocytes that apparently had penetrated the pleural surface and were packed within the serous membrane. There was no instance in which the diaphragmatic lymph vessels were filled nor did lymph spaces between the muscle fibers contain graphite in any form. It was evident that the diaphragm is not an efficient drainage mechanism for the pleural space. The contrast between this and the behavior of the diaphragm with relation to drainage from the peritoneal space was striking.[2]

In contrast to this sluggish or negative reaction of the diaphragmatic and visceral layers of the pleura and the apparent lack of drainage from the pleural cavity through the lymph channels of the lung, the mediastinum and all its subdivisions as well as the regional lymph nodes related to it assumed the most remarkable signs of activity. In every instance, even in experiments lasting but 1 hour, the mediastinum became densely colored and the anterior mediastinum hung like a black curtain between the two sides of the thorax. There was a peculiar adhesive quality about the mediastinum that

seemed to attract the irritating material to itself. Almost invariably the mediastinum was not only thickened but formations of large exudative masses were attached to it; these were firmly adherent to both sides of the mediastinum as well as to the pulmonary ligaments. When examined in the early stages they consisted largely of graphite-laden polymorphonuclear leukocytes, comparable to those appearing in the effusion. In the earlier observations free graphite was identified among the mesothelial cells of the mediastinum; erythrocytes were numerous, and evidence of phagocytosis was observed in the polymorphonuclear leukocytes as well as in the nongranular mononuclear phagocytes. In later stages changes in the mediastinal tissue occurred much as in the parietal pleura. The cellular inflammatory reactions such as hyperæmia and edema gradually disappeared and subsequent organization of the tissue occurred gradually. Capillary invasion took place, fibroblasts appeared in larger numbers with the result that new connective tissue invaded these exudative masses. The fibroblasts themselves were similar to those usually seen in the early constructive processes terminating in the formation of fibrous tissue. The phagocytic nongranular mononuclear cells appeared to change from round to elongated cells resembling fibroblasts. These retained the ingested graphite and it served to distinguish them from fibroblasts which appeared to lack the function of phagocytosis.

Regardless of the time the animal was permitted to live, the mediastinum remained black throughout life. In all of the experiments and in the many observations and dissections that were made, there was no evidence to show that actual lymphatic vessels were present in the anterior mediastinum or that the anterior mediastinum assisted in the transference of fluid and particulate matter from the pleural space. There are many suggestive facts, however, which would lead to that conclusion and further work is being done in the hope that the rôle of the mediastinum as a transferring mechanism can be established. It seems probable that it occupies the same place in pleural absorption that the omentum does in peritoneal absorption.[1] There is no question but that the mediastinum is a protective mechanism, absorbing large quantities of any irritating material which may be present, retaining it as though it were included in a sponge and finally fixing it within itself by the production of connective tissue.

In no single experiment were all of the lymphatic tracts completely delineated, and the description that will follow is a composite of all of the observations made in the separate experiments. A standard description is given, however, showing observations commonly encountered in an experiment of short duration.

Typical Experiment. An animal was fed 75 cc. of butter and cream, stained with Sudan III, at 8.15 A.M. Sixteen cubic centimeters of graphite suspension was immediately injected into the right side of the thorax and

necropsy was done at 11.15 A.M., exactly 3 hours after the beginning of the experiment. When the abdomen was opened the cisterna chyli was distended with pink lymph and the lymphatic radicles of the mesentery were deep pink. The thoracic duct itself contained pink lymph and it could be traced to the lymphatic venous confluence. Lymphatics were not visible on the pleural surface of the diaphragm. This constant negative observation lends assurance to the belief that the diaphragmatic lymphatic system has to do only with the removal of peritoneal exudates. Examination of the lymph nodes revealed that the retroperitoneal node, dorsal to each kidney, was densely black and the lymphatic tracts leading backward from the posterior wall of the thorax was readily seen passing beneath the lumbar attachment of the diaphragm into the retroperitoneal space, and leading directly to this node. Exceedingly small lymph vessels passed from the node into the cisterna chyli. A similar picture occurred on both the right and left sides. The nodes in relation to the spleen were also slightly dark, although there was a question whether this was actually due to pigment. It has been shown that in a certain percentage of dogs lymph vessels pass from the diaphragmatic pleura posteriorly over the surface of the cardia to a lymph node in the hilum of the spleen. This is the only suggestion we have that the diaphragmatic pleura may have absorbed particulate material. No other lymphatic nodes in the abdomen were black. On opening the thorax, one is impressed by the fact that the dog has literally a single thoracic space and that generalized inflammation occurs rapidly after the insertion of an irritant into the pleural cavity. Thirty cubic centimeters of a black serous effusion was removed from the right side and approximately an equal amount was taken from the left side. Smears made of the fluid contained many erythrocytes and leukocytes. Some free graphite was found and the polymorphonuclear cells had already phagocytosed many granules of pigment. There were relatively few monocytes, but they also contained large quantities of pigment, packed into large granules. The visceral pleura was entirely free of any evidence of inflammation and, although both lungs were bathed in this black serous effusion, there was no evidence that the visceral pleura had absorbed pigment. Even the nodes of the hilum of the lung were not abnormally dark. The conclusion was clear that the lymphatics of the lung and visceral pleura have little, if anything, to do with the removal of such particulate material from the pleural space. The conclusion was also apparent that the material was picked up by the cells of the costal pleura, and the cells of the mediastinal pleura as well as by the pulmonary and the pericardial ligaments. There seems to be no other explanation than that the pigment passed into these mesothelial structures and then entered their related lymphatic vessels and passed into the lymph nodes in the anterior and posterior mediastinum.

On both sides the backward flow of lymph into the retroperitoneal space, dorsal to the kidneys, could be seen definitely. These lymph channels arose in the dorsal costal pleura about the level of the tenth rib; on both sides, the forward lymph flow started in the interval between the ninth and tenth ribs. On the left side a single lymph vessel passed forward parallel to the sympathetic nerve trunk as far as the level of the third rib, where it divided into two, one of which passed over the thoracic duct and the esophagus and entered a large and elongated densely black lymphatic node along the esophagus. The larger branch continued forward, crossed the sympathetic nerve trunk and divided into three branches, two of which passed into the upper pole of the same lymph node, and the third, forward over the dorsal anterior wall of the thorax. The upper of the two branches entering the node divided into two, the superior of which proceeded forward to enter into a second smaller lymph node. The efferent vessels from the

nodes were joined in their course toward the entrance into the thoracic duct by afferent vessels from the sternal nodes which ran parallel to the internal thoracic artery. The intercostal segmental lymph vessels entering this longitudinal tract were not encountered in this experiment.

On the right side of the thorax the pattern made by the forward-flowing lymph vessels was more intricate than on the left. Only 2 vertebral lymph nodes were present, 1 in the eighth and 1 in the fourth interspace, and both lateral to the azygos vein, between it and the sympathetic trunk. A long collecting lymph vessel received the segmental lymph vessels from the interspaces as tributaries, thus uniting these 2 nodes. Vessels from the third and fourth interspaces also were afferent to the upper of the 2 vertebral nodes from which efferent vessels formed a plexus on the surface of the trachea. (Fig. 1.) Their course upward was interrupted by several small tracheal lymph nodes. Finally the plexus united in 2 larger tracheal nodes lying opposite the head of the first rib. Lymph tracts from these nodes communicated with tracheal nodes on the opposite side; others united with the lymph vessels, passing upward through the mediastinum parallel to the internal thoracic artery and then proceeded to the venous confluence on the right.

The backward course of the lymphatics posterior to the ninth rib into the retroperitoneal space was readily made out. (Figs. 2, 3 and 4.) There was no question about the existence of these lymph vessels; they could be seen just as well as veins or arteries and could be traced throughout their course to the point at which they joined the superior pole of the lymph node. From this node the connection with the cisterna chyli was easily seen. By using a colored medium and injecting directly into the node, the cisterna as well as the thoracic duct was completely filled and the venous confluence was identified. By the same method, however, the afferent vessels to this node were not injected, since the strength of their valves protected against a reverse flow and the vessels ruptured before the valves were overcome.

The sternal lymph nodes were densely black and the anterior mediastinum hung as a black curtain between the pleural spaces. Festoons of black exudative material hung from this central partition. Efferent channels from the sternal lymph nodes passed onward parallel to the internal thoracic bloodvessels toward the lymphatic venous confluences. On the left side they united either directly with the thoracic duct or indirectly after union with efferent vessels from the tracheal lymph nodes and on the right they combined with efferent vessels from the tracheal lymph nodes and passed to the right cervical lymphatic confluence.

Lymph Nodes of the Thorax of the Dog. On the basis of our study, the lymph nodes of the thorax in the dog may be divided into parietal lymph nodes associated with the drainage of the thoracic wall, and visceral lymph nodes associated with drainage of the thoracic viscera.

Parietal Lymph Nodes. These nodes fall into 3 groups, the sternal, the vertebral and the diaphragmatic.

A certain latitude of variability may always be assumed in describing any portion of the lymphatic system; this same observation holds true concerning the sternal nodes. In all the animals we have examined there were 1 or 2 sternal lymph nodes on each side, immediately anterior to the border of the triangularis muscle at the level of the first rib. In some animals, however, this simple arrangement was replaced by a chain of 2 or 3 lymph nodes, close to the sternum and approximately at the level of

the first and second ribs. They were in all instances closely approximated to the internal thoracic bloodvessels.

The vertebral nodes were very small and extremely variable in their arrangement. As a rule, these nodes were not identified; at other times, 1 or 2 very small nodes were found just lateral to the sympathetic trunk and usually in the interspaces between the heads of the ribs. Segmental nodes were not identified in each interspace, although when present they received the drainage from the segmental intercostal lymph vessels. There was, however, a rather more segmental distribution on the right side, and it was not uncommon to find a node of varying size either above or below the entrance of the azygos vein into the vena cava. In some animals 2 nodes were present at this site, 1 above and 1 below the confluence of the azygos vein and vena cava. Occasionally very small lymph nodes were found lateral to the azygos vein in one or more of the interspaces as low as the eighth, but such segmental nodes were never seen below the eighth interspace.

In most of the animals studied lymph nodes were not seen on the pleural surface of the diaphragm. In others a group of very small nodes was identified at the insertion of the phrenic nerve into the diaphragm. Evidently they are less well developed in the dog than in primates. Scott and Beattie described 2 or 3 small nodes lying on the central tendon of the diaphragm and usually surrounding the inferior vena cava. They found these nodes constant in apes and in larger old-world monkeys, but frequently absent in smaller monkeys. In South American monkeys they are variable or absent in the smaller members of the group.

Visceral Lymph Nodes. The visceral nodes may be divided into 4 groups: mediastinal, pulmonary, tracheobronchial and tracheal. We shall not describe the pulmonary lymph nodes because they appear to play a small part in the removal of particulate matter or fluids from the pleural space. Scott and Beattie distinguished between the mediastinal and the tracheobronchial nodes, and remarked that it was common in pathologic literature to confuse these nodes. They felt that the nodes are often called mediastinal when they should be called tracheobronchial: "The 2 groups are distinct and can be readily differentiated by the fact that the tracheobronchial group is always pigmented with carbon particles in animals living in city atmosphere while the mediastinal glands remain clean."

The mediastinal nodes comprise 3 or 4 small nodules which lie either ventral to the superior vena cava, or between the veins and the trachea. Usually they are very small and in our experience were not at all constant. The tracheobronchial nodes (Fig. 5) were in the superior and inferior angles formed by the division of the trachea and were fairly large. In our observations the tracheal nodes were variable in number and in position. There were 3 or 4, however, on the right side, that were fairly large and quite constant in position. One was cephalad to the confluence of the azygos vein with the vena cava, another was at the origin of the vena cava at the point of confluence of the large innominate veins and a third was lateral to the jugular vein in the first interspace. To the right of the vena cava the right surface of the trachea was visible, and on it there was frequently a group of small lymph nodes.

On the left side the arrangement of the nodes was similar but they were invariably smaller. A communication of the two sides between the 2 tracheal groups was observed by way of small lymphatic channels. The most common arrangement on the left side consisted of 1 node immediately above the arch of the aorta and 1 above and 1 below the origin of the internal thoracic artery.

Lymphatic Vessels of the Thorax of the Dog. These may be conveniently divided into two systems draining the right and the left sides. On both sides, the subdivision may further be carried into dorsal and ventral. The dorsal division may again be divided into an upper and lower subdivision.

When the graphite was introduced into the thoracic cavity, it soon became adherent to the parietal or costal pleura and usually was indefinitely distributed beneath the pleural surface. The pleura had a smoky appearance, and although the distribution was indefinite, yet in the main the discoloration occurred in parallel lines above and below the margin of the ribs. This characteristic distribution was present throughout the extent of both the dorsal and the ventral portions of the costal pleura.

Dorsal Distribution. Dorsally the distribution of the upper lymphatic vessels had a fairly characteristic pattern, but had certain distinct differences on the two sides. On the right from the eighth interspace to the fourth interspace the segmental lymphatic radicles passed into a collecting vessel which continued forward to the lymph nodes that have been described in relation to the azygos vein. (Fig. 1.) Then afferent channels passed upward, forming a plexus over the right ventral surface of the trachea to the upper tracheal nodes when the drainage continued to the right venous confluence. The efferent vessels from the tracheal nodes were joined by efferent tracts from the sternal lymph nodes and entered the cervical lymph duct at its jugular confluence. The usual drainage encountered above the third interspace formed a pattern which was less segmental. The collecting radicles passed forward and entered directly into 1 of the 2 upper tracheal lymph nodes. In only 1 instance, however, the radicles from this region coursed downward to join with the collecting trunk, that had passed forward from the eighth interspace; usually the flow in the vessels of the upper interspaces was upward to the two upper tracheal lymph nodes.

The arrangement of the collecting vessels at the upper division of the dorsal costal pleura on the left side was less complicated and usually consisted of a single vessel arising in the eighth or ninth interspace. This unpaired lymph vessel passed forward lateral to the sympathetic trunk until it reached the level of the third rib, when it inclined toward the median line, crossed to the esophagus and broke up into a plexus of varying patterns. It finally entered the lymph nodes on the esophagus previously described and then coursed forward and to the left, to join the efferent vessels from the sternal nodes. The lymph drainage from the sternum, mediastinum and costal pleura united with the thoracic duct just before it reached its confluence with the vein. With one exception, segmental intercostal branches never entered the thoracic duct. This description is somewhat different from that of Scott and Beattie, but their work was done on primates including the chimpanzee and the monkey (Macacus rhesus).

The drainage system of the lower dorsal costal pleura on both sides was formed by a number of small vessels which coursed downward, receiving lymphatic radicles from the tenth, eleventh and twelfth interspaces. (Fig. 2.) These were usually arranged in groups of 3 or 4 vessels which passed dorsal to the pars lumbalis of the diaphragm to a lymph node in the retroperitoneal space just above the upper pole of the kidney. This node, in turn, was connected by lymphatic vessels to the cisterna chyli.

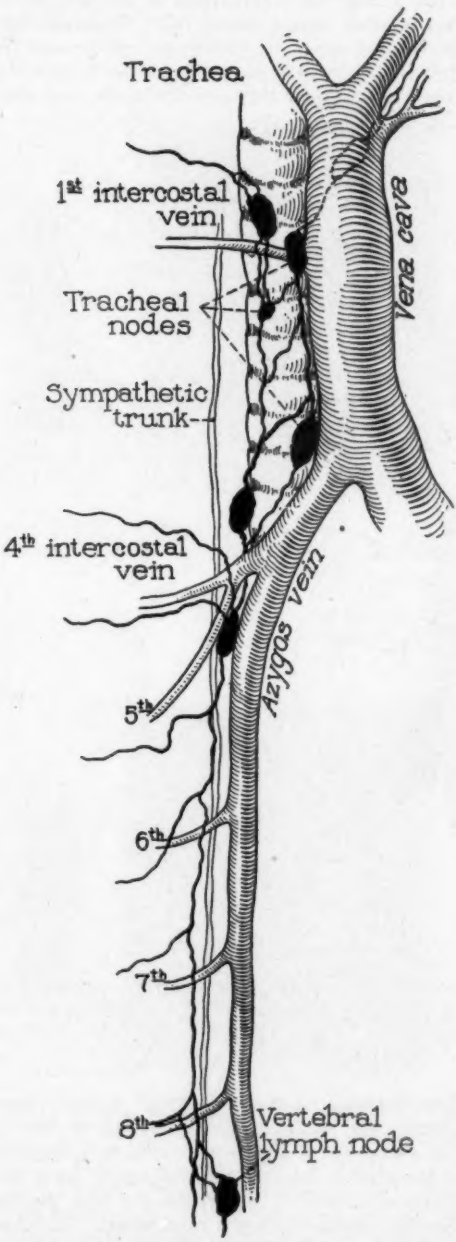

FIG. 1.—Distribution of lymph nodes and segmental lymphatics, the collecting lymphatic vessel and the lymph nodes and plexus of lymphatics in relation to the trachea.

If the diaphragm on the right side was stripped of its attachment and the liver and the kidney were retracted to the left, as in Fig. 2, the vessels could be traced in their entire course from the lower interspaces backward to the retroperitoneal space to the lymph node and then to the cisterna chyli. In a few instances this plexus from the thorax emptied directly into the cisterna before it passed through the node, but this arrangement was unusual. (Fig. 2.)

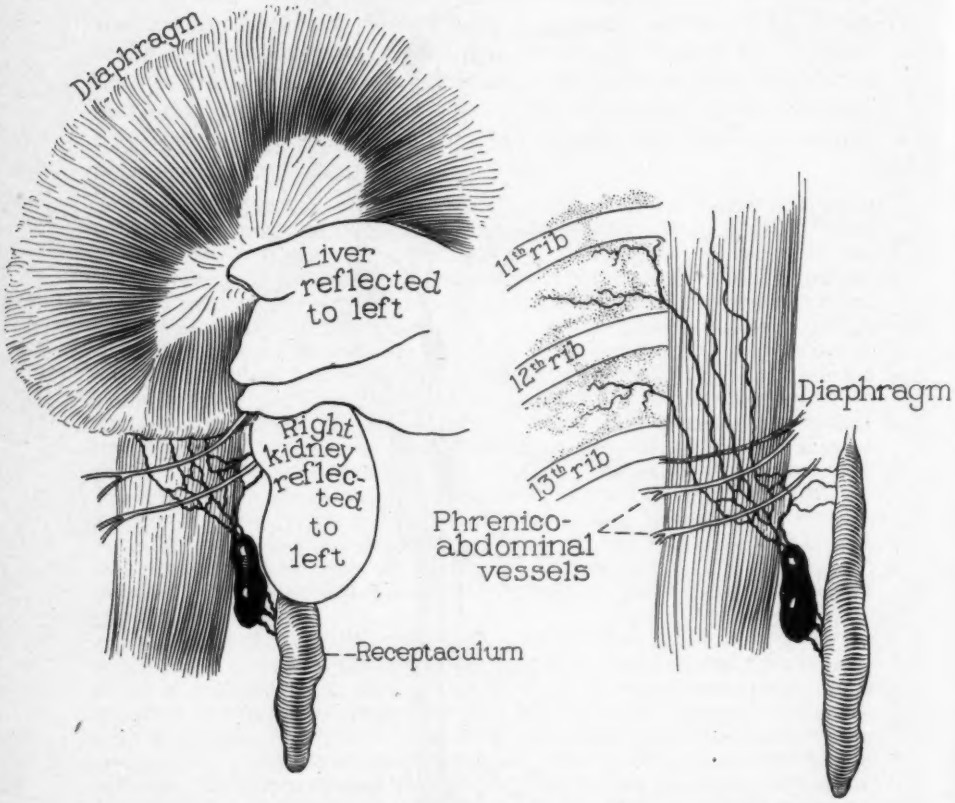

FIG. 2.—The backward course of the lymphatics, posterior to the ninth rib into the retroperitoneal space. The vessels unite in a plexus before they enter the retroperitoneal lymph node dorsal to the kidney. From it efferent vessels enter the cisterna chyli.

Ventral Distribution. Ventrally, small lymph vessels were disclosed beneath the transverse thoracic muscles close to the juncture of the ribs with the costal cartilages. These were followed distally along the anterior and posterior margins of the ribs and appear to have the same distribution as the indefinite infiltration, described for the pleura. These channels acted as collecting vessels for each interspace. They passed mesially and anteriorly somewhat parallel to the ribs, usually with a single vessel both above and below the margins of the rib, and finally beneath the transverse thoracic muscle they united to form an intricate lymphatic plexus. (Fig. 6.) The plexus was always lateral to the internal thoracic bloodvessels. It was

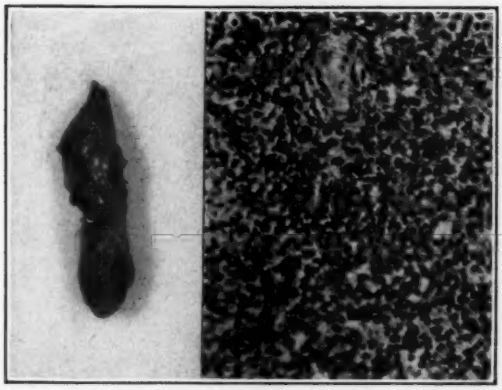

FIG. 3.—Gland dorsal to kidneys. The white gland was removed the day previous to intrapleural injection of particulate matter; absence of any pigment is shown. (× 200.)

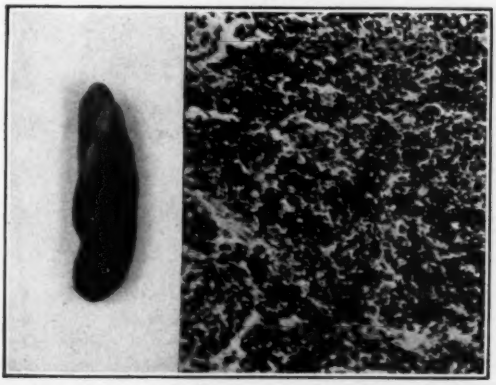

FIG. 4.—Gland dorsal to kidneys. The black gland was removed 12 hours after intrapleural injection of graphite suspension. The black gland shows the presence of large amount of pigment.

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not connected with the lymphatic plexus which carried absorbed materials from the peritoneal cavity, but was a distinct plexus and was employed only in the drainage of the ventral parietal pleura. These collecting vessels, comprising the sternal plexus, passed into the sternal lymph node which was situated anterior to the internal thoracic bloodvessels, approximately opposite the third costal cartilages. Anterior to this rib the lymphatics of the interspaces and of the pleura covering the operculum emptied into the anterior of the 2 sternal lymph nodes opposite to or above the first rib. On the right side this arrangement was usually more easily seen and the vessels were larger than those on the left side. The plexus, too, was always more complicated.

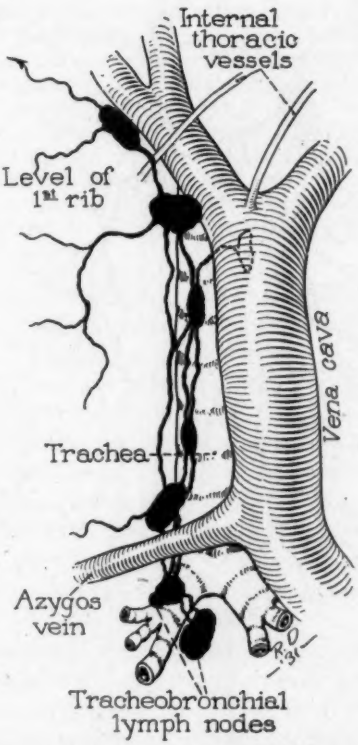

FIG. 5.—The position of the superior and inferior tracheobronchial lymph nodes and their relationship to the drainage system of the upper portion of the posterior costal pleura of the right side.

Microscopic Appearance of the Liver, Spleen and Lymph Nodes. In the pleural effusions that formed following an injection, free particulate matter was always present if only short periods elapsed between injection and exploration. This was true in experiments of five hours' duration, and in 1 experiment of 18 hours' duration. The sternal and the tracheal lymph nodes were always densely black within 1 hour. The retroperitoneal node, in relation to the kidney, became black usually within the second hour. It was obvious, then, that the lymph drainage occurred promptly and that free particulate matter was distributed into the lymph nodes together with that contained within the phagocytic cells both of the polymorphonuclear and the monocytic types. Furthermore, it appeared that the material

absorbed and transferred through the lymphatics reached the thoracic duct or the right lymphatic duct and emptied into the venous circulation within a period of approximately 1 hour; it thus became possible for such particulate material to reach the systemic circulation and to appear in the liver, spleen and bone marrow within a relatively short time after injection. On examination, grossly, of a large number of livers and spleens, there was no evidence of discoloration from pigment. On microscopic section, however, two characteristic reactions were manifest. In those examined

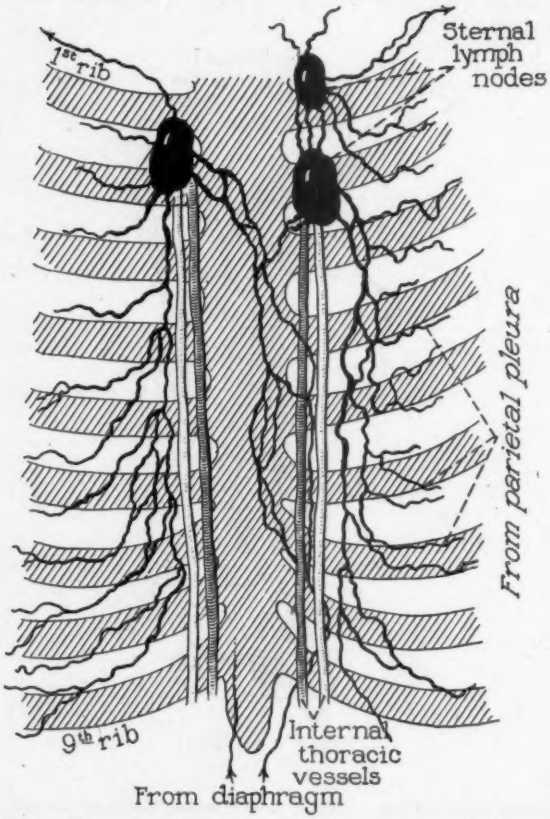

FIG. 6.—The lymphatic drainage system of the anterior costal pleura. It consists of segmental vessels uniting in a complicated plexus of vessels beneath the transverse thoracic muscles. The plexus is lateral to the internal thoracic vessels and independent of the plexus of lymphatics concerned with the drainage of the peritoneal cavity. The intermingling of the lymph from the two drainage systems takes place in the sternal nodes.

within 2 to 3 hours of the injection, the Kupffer cells were swollen to several times their original size, and they encroached on the lumen of the sinusoids, or desquamated into the lumen. This appearance always preceded the recognition of particulate matter within them. It would appear that the irritating action of the intrapleural injection was manifest following absorption and that irritation was induced within the liver preparatory to the phagocytic activity by the Kupffer cells. Particulate

matter, however, was never encountered free in the hepatic sinusoids. It was evident that the liver contained a larger amount of the absorbed material than did the spleen. Here again, however, when present it was contained within the reticular cells of the splenic sinuses. The blood spaces did not contain free pigment and phagocytic cells containing pigment free within the sinuses were not encountered.

In the sternal and the tracheal nodes, or in any of the nodes in the path of drainage from the thorax, a similar picture was invariably seen. If the experiment had lasted more than 2 or 3 hours the picture varied somewhat, but generally the graphite was distributed throughout the entire node. Often the lymph follicles, immediately beneath the capsule, contained graphite which was always included within large nongranular mononuclear phagocytic cells. Occasionally graphite was seen free in the lymph sinuses or often in large mononuclear cells which had either entered the node from the draining lymph channels or had desquamated from the reticular syncytium. The dense blackening of the lymph node was due to the marked phagocytic activity of the littoral cells lining the lymphoid sinuses. They were often literally packed with free graphite material. There was no evidence of circulating granules or of phagocytosis among the cells of the blood stream within the lymph nodes, and thus it seemed obvious that the distribution within the nodes was truly drainage through the lymphatic system.

Summary. Experiments, in which a graphite preparation was injected into the pleural space of dogs, produced an inflammation and delineation of lymphatic vessels solely by the natural method of absorption and drainage. This provides a means for the study of the functional lymphatic system of the dog's thorax and therefore includes the lymph nodes and the afferent and efferent lymph vessels in their normal position and usual distribution.

The lymph nodes in the thorax of the dog arrange themselves naturally into two main groups: parietal and visceral. The parietal group comprises the sternal, the vertebral and the diaphragmatic nodes; the visceral group includes the mediastinal, pulmonary, tracheobronchial and tracheal nodes.

Of the parietal lymph nodes, those of the sternal group, which lie at the level of the first and second interspace and receive the lymph drainage from the peritoneum, as well as from portions of the costal pleura, are the most constant in number, size, and position. The vertebral nodes are fairly inconstant in dogs. When present they lie on the intercostal muscles beneath the costal pleura just lateral to the thoracic sympathetic nerve chain. We have never identified a completely segmental distribution of vertebral lymph nodes in dogs. They are usually more commonly found on the right side than on the left. Diaphragmatic nodes are perhaps more rarely encountered than vertebral nodes. When present they lie on the tendon or near the insertion of the phrenic nerve into the muscle.

Of the visceral group of lymph nodes the mediastinal are perhaps the most inconstant. They comprise a group of three or four small nodes which lie ordinarily between the vena cava and the trachea. The lymph nodes of the tracheobronchial group are invariably

constant in size and usually in number. They lie in the superior and inferior angle of the tracheal bifurcation. The extent and distribution of the tracheal nodes are exceedingly variable. They vary in number from three to six and lie along the trachea from the juncture of the azygos vein and vena cava to the level of the first interspace.

The lymph drainage associated with these nodes may be grouped into six routes, two of which conduct lymph caudad and four cephalad. The line of cleavage, so called because it represents the level on the dorsal wall of the thorax from which lymph flows cephalad and caudad, is at the level of the eighth or ninth interspace. From this level, on both right and left sides, lymph vessels pass caudad, and empty into a large lymph node which lies dorsal to the anterior pole of each kidney. Efferent vessels from these nodes lead directly into the cisterna chyli. The cephalad lymph drainage from this cleavage plane along the dorsal median line is less easily demonstrated than the caudad one. Intercostal segmental collateral vessels are not constant, although far more nearly so on the right than on the left side. On the right the collecting channels empty into the caudad tracheal group of nodes; on the left, into the mediastinal group of nodes.

On each side of the sternum the lymphatic drainage system from the ventral pleura comprises a series of segmental channels which converge to form an extensive plexus lateral to the internal thoracic bloodvessels beneath the transverse thoracic muscle. This plexus is lateral to the one which carries lymph from the diaphragm to the sternal nodes. Both pleural and abdominal lymph draining the plexus, empty into the sternal group of nodes at the level of the first and second interspaces. In the course of the lymphatic vessels through both the anterior and the posterior mediastinum communicating lymph channels permit the interchange of lymph from the two sides of the thorax. The terminal efferent vessels from the sternal and the tracheal nodes usually become confluent and together join the thoracic duct or the right lymphatic duct proximal to the lymphatic venous confluence.

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REVIEWS.

A Text-book of Pathology. By William Boyd, M.D., M.R.C.P. (Ed.), F.R.C.P. (Lond.), Dipl. Psych., F.R.C.S., Professor of Pathology in the University of Manitoba; Pathologist to the Winnipeg General Hospital. Pp. 946; 287 engravings and a colored plate. Philadelphia: Lea & Febiger, 1932. Price, $10.00.

This book is avowedly a textbook for undergraduate and postgraduate students, not a reference book for professional pathologists, and the author has intended to limit himself to treating of the fundamentals. Notwithstanding this avowal, many of the very newest notions are discussed, especially those which seem to the author to add to our knowledge of functional pathology. His stress on the functional aspects and his short résumés of clinical symptoms aid the student in correlating the various preclinical branches of medicine with each other and in correlating the pathological with the clinical aspects of disease. In doing this the author in no way detracts interest from the morphological details. He says, "morbid anatomy is not dead and never has been, except in the hands of those whose dull minds would take the breath of life from the most vital subject," and the present volume bears witness to the truth of that statement because the author's vivid imaginative style of writing gives color and emphasis of details, and his personal enthusiasm for his subject must prove infectious to many a listless student. In fact, this book is felt to be a very emphatic and personal expression.

The Reviewer does not agree with some of the author's convictions about certain perplexing points in the etiology and pathogenesis of various conditions, or with his apparent reliance on certain recent experiments, or with some of his philosophical persuasions; but these personal points of view are always interesting and may be differentiated from the statement of proved facts. The author may seem too dogmatic on points that some would consider debatable, but as the book is intended for students he doubtless prefers to run the risk of erring in this respect, rather than to confuse the student with hair-splitting of minor details, between which the more experienced reader should be able to discriminate.

The sections devoted to special pathology (about two-thirds of the book) are much less detailed than the author's treatment of the same subjects in his "Pathology of Internal Diseases." The illustrations are largely photomicrographs, many being the same as in the other work, are well selected and technically excellent. More references are to British literature than is usual in American textbooks. I. Z.

Diabetes in Childhood and Adolescence. By Priscilla White, M.D., Physician at the New England Deaconess Hospital, Boston. With a Foreword by Elliott P. Joslin, M.D., Clinical Professor of Medicine, Harvard Medical School; Consulting Physician, Boston City Hospital. Pp. 236; 25 illustrations and 1 colored plate. Philadelphia: Lea & Febiger, 1932. Price, $3.75.

The story of the diabetic child is one of the bright pages of modern medicine. In the pre-insulin era the life expectancy of the diabetic child

was 2 years at most. With insulin, 76 children in Dr. Joslin's series have lived 10 years or more. Furthermore, the experience with the diabetes of childhood is helping to solve some of the important problems of the disease in adults, notably arteriosclerosis. Dr. White, who has been in contact with Dr. Joslin's Clinic since before the introduction of insulin, has presented in a clear and interesting manner all the details of the management of the youthful diabetic through childhood and adolescence into adult years. She has adduced convincing evidence on the hereditary factor in the disease. The book is a worthy addition to the others which have come from the Joslin Clinic and it should be in the hands of every practitioner of medicine. R. K.

INFECTIONS OF THE KIDNEY. By MEREDITH F. CAMPBELL, M.D., F.A.C.S., Attending Urologist, Babies Hospital, New York Nursery and Child's Hospital; Assistant Visiting Urologic Surgeon, Bellevue Hospital, New York. Pp. 343; 40 illustrations. New York: Harper & Bros., 1931. Price, $3.00.

THIS is another of Harper's Medical Monographs, a series of convenient pocket-size works for practitioners. The present volume is quite up to the high standard of excellence set by the volumes which have so far appeared. Not intended as a reference book, the material has been presented concisely, without bibliography and with the practical interest of the reader constantly in view. The chapters on anatomy and physiology, on methods of examination, on perinephritic abscess and on renal infection in infancy and childhood should be particularly helpful. The author has unfortunately failed to include the urea clearance test in the discussion of kidney function testing. R. K.

ASTHMA AND HAY FEVER IN THEORY AND PRACTICE. In three parts. *Part I. Hypersensitiveness, Anaphylaxis, Allergy.* By ARTHUR F. COCA, M.D., Professor of Immunology, Cornell University Medical College. *Part II. Asthma.* By MATTHEW WALZER, M.D., Instructor in Applied Immunology, Cornell University Medical College. *Part III. Hay Fever.* By AUGUST A. THOMMEN, M.D., Lecturer in Medicine, University and Bellevue Hospital Medical College. Pp. 851; 95 illustrations and 7 charts. Springfield, Ill.: Charles C Thomas, 1931. Price, $8.50.

FROM the standpoint of the student of the phenomena of hypersensitiveness, this is beyond doubt the best book which has appeared on the subject. All three authors bring to their task a thorough knowledge of, and long experience with, the subject. They have spared no pains in setting forth every phase of the subject in the greatest detail. They have surveyed and judiciously culled an extensive literature (over 2000 references). The result is a volume that is truly encyclopedic in its scope. Those working in the field of Allergy cannot afford to be without it. The excellent arrangements of the material and a well-prepared and extensive index make the information easily available to the student and practitioner, so that those not especially concerned with this field need not fear being bogged down by unnecessary detail. After these superlatives the Reviewer will be pardoned if he points out that Dr. Walzer seems at times to tilt rather quixotically against bronchospasm as a factor in the mechanism of bronchial asthma, and that Dr. Coca seems to have adopted a somewhat kindlier view than formerly toward the cutaneous method of testing. He even finds that

with a specially concentrated house-dust extract it is possible for the first time to get positive reactions by the scratch method—we have been doing so to our own satisfaction with a 14 per cent alcoholic extract for the past 11 years. But these are quibbles. The fact remains: this is the number One book in allergy. R. K.

RECENT ADVANCES IN ALLERGY. By GEORGE W. BRAY, M.B., CH.M. (SYDNEY), Asthma Research Scholar, The Hospital for Sick Children, London. With Foreword by ARTHUR F. HURST, M.A., M.D. (OXON.), F.R.C.P., Senior Physician, Guy's Hospital; Chairman Medical Advisory Committee, Asthma Research Council of Great Britain. Pp. 432; 98 illustrations, including 4 colored plates. Philadelphia: P. Blakiston's Son & Co., Inc., 1931. Price, $3.50.

BUT merely a review of recent literature as its title would suggest, this book is a well-rounded treatise on allergy. It is the first European book, certainly the first from the British Isles, which is in accord with the views on allergy which are current in this country. The author has also drawn on his own observations in a large number of asthmatic children. The only disadvantage of the book from an American standpoint is its lack of surveys of plant and pollen distribution. R. K.

QUANTITATIVE CLINICAL CHEMISTRY. VOL. II, METHODS. By JOHN P. PETERS, M.D., M.A., Professor of Internal Medicine, Yale University School of Medicine, and DONALD D. VAN SLYKE, PH.D., SC.D., Member of The Rockefeller Institute for Medical Research. Pp. 957; 95 illustrations. Baltimore: The Williams & Wilkins Company, 1932. Price, $10.00.

THIS second part of this important work deals with descriptions of the various laboratory procedures concerned with substances studied in clinical diagnosis and therapy (For Review of Part I on Interpretations, see AM. J. MED. SCI., 1931, **182**, 275). In general the authors have presented as far as possible gravimetric, titrimetric, colorimetric, and gasometric methods with macro and micro forms, for the numerous substances to be tested. Furthermore they have prefaced each chapter with a discussion of the principles on which the methods are based. The details of Procedure have been printed in black face type, greatly adding to convenience of use. The 32 chapters cover such a breadth of material that space forbids any attempt at detailed description; the excellence of the treatment of the material renders any attempt at critical analysis both superfluous and presumptuous. One can safely say that clinical chemistry will have to make radical changes indeed before these two volumes cease to be indispensable to the student, the clinician and the laboratory worker. E. K.

PROHIBITING MINDS. By STEWART PATON, M.D., Lecturer on Psychiatry, Johns Hopkins University, Baltimore. Pp. 198. New York: Paul B. Hoeber, Inc., 1932. Price, $2.00.

A SCIENTIFIC and experienced student of human behavior here shrewdly analyzes the various factors that have led to our present "waves of prohibiting mania." Today's squandered supplies of nervous energy, together with the reluctant recollections of foolish performances by both individuals

and masses, and unwillingness to profit from past mistakes and adapt to present conditions—such forces impel "these feelers, not thinkers" to hate and to try to prohibit anything that runs contrary to their own restricted activities. Such thoughts furnish the author with the material for the first half of his book. Occasional remarks such as "At least three-fourths of the population of the United States are, have been or will be subjects of emotional disorders of sufficient intensity to attract public attention" indicate the gravity of the subject dealt with. The three chief examples of prohibitionism that he discusses are the attempts to regulate the affairs of the Prussian state, Russian communism and the liquor traffic in this country—all failures which drag other evils in their train.

In the last constructive half of the book the author offers his remedies, based on deliberate sustained efforts to "learn to use his mind to help him live more rationally." The acquisition of more self-control and adaptability will lead to a restored confidence in ability to meet our problems with a corresponding diminution in the prohibiting mania. A thoughtful reading of this penetrating essay is earnestly recommended to those in all walks of life. E. K.

MENTAL HEALERS—MESMER, EDDY AND FREUD. By STEFAN ZWEIG. Pp. 363. New York: The Viking Press, 1932. Price, $3.50.

THIS distinguished illustrator and critic of human types has here engaged to "portray ideas as embodied in certain human lives" identified with bold departures in mental healing. Mesmer, discoverer of the principle of suggestion as strengthening the will-to-health, though he never thoroughly understood his own discovery; Mrs. Eddy, charming away pain and sickness by an ecstasy of faith; and Freud, removing hidden mental conflicts by bringing them into the field of consciousness by the method of psychoanalysis—these three the author without intended partisanship presents as types that have brought healing to many thousands. Most appropriate, therefore, is his quotation from Paul Valery: "The world becomes of value only through extremes but it exists only thanks to mediocrity."

Fortunately, for the interest of the tale, it was not possible to maintain the neutral position that the author aimed at. Mesmer is convincingly presented as a maligned philanthropist, the first of the new psychologists in advance of his time, suffering through the ancient and "inexorable commandment that firstlings shall be sacrificed." The account of Mrs. Eddy, lying between Miss Wilbur's "rose-colored biography" and Miss Milmine's now almost unprocurable detraction, should share with Dakin's "Mrs. Eddy" as an impartial evaluation of the numerous shortcomings yet invincible strength of a woman of genius who carved a position for herself equal in power to Queen Elizabeth or Catherine the Great. For Freud, the author becomes frankly partisan, regarding him as the first to have the insight, sincerity and courage to depart from the ostrich policy of nineteenth century morality of hiding sexual topics that would not down.

But, while granting the value accruing from Mrs. Eddy's extremes, the author is unsparing of her weaknesses and errors; in the case of Freud he is so in sympathy with the method of relieving suppressed impulses by raising them to the field of consciousness that he overlooks the Freudian exaggerations of Œdipus, narcissistic, castration and other sexual complexes that so mutilate Freud's doctrine and alienate supporters. Exploration of the "unconscious," no longer the "unknowable," is recognized as Freud's "supreme act of genius," which is regarded as altering all the standards of our mental dynamics, and as a creation ranking in importance in the story of human knowledge with those of Copernicus and Kant. Perhaps from the exuberance of its partisanship, the exposition of Freudism is the least convincing of the three. E. K.

BIOCHEMISTRY IN INTERNAL MEDICINE. By MAX TRUMPER, PH.D., Clinical Chemist and Toxicologist, Jefferson Medical College and Hospital, and ABRAHAM CANTAROW, M.D., Instructor in Medicine, Jefferson Medical College. With a Foreword by ELMER H. FUNK, M.D., Sutherland M. Prevost Professor of Therapeutics at Jefferson Medical College. Pp. 454; 11 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, $5.50.

"IT should be emphasized, that the clinical value of biochemical data depends, first, upon the accuracy of the methods and skillful technique in the laboratory and, second, upon the rational clinical interpretation of the laboratory findings at the bedside. The practising physician is not, as a rule, interested in the first, but he should be well informed regarding the clinical interpretations. This book will serve as a guide. It is generally recognized that considerable skill is required of the physician in the use of laboratory aids to diagnosis and in their proper interpretation in relation to clinical phenomena." "The advancement of our knowledge of the biochemical changes in health and in disease has been most rapid and many of the conceptions of a few years ago have been completely changed or modified. This book will serve to acquaint the practitioner with the recent advances, many of which are to be found only in special monographs and textbooks." (Quoted from Dr. Funk's Foreword.)

MAN AND MICROBES (A CENTURY OF PROGRESS SERIES). By STANHOPE BAYNE-JONES, M.D., Professor of Bacteriology, School of Medicine and Dentistry, University of Rochester. Pp. 128; 17 illustrations. Baltimore: The Williams & Wilkins Company, 1932. Price, $1.00.

THE Century of Progress Series is the outcome of the efforts of the Advisory Committee of the National Research Council to aid the Century of Progress International Exposition in recording as well as depicting the last hundred years of intellectual activity. Here the story of microbes is told in a simple yet accurate manner, in their relation not only to human disease but to agriculture, industry and diseases of animals, plants and insects. Though written primarily for the general reader, it affords not a little that will be new to the average medical reader.

E. K.

INTRACRANIAL TUMORS. By HARVEY CUSHING, Professor of Surgery, Harvard Medical School; Surgeon-in-Chief, Peter Bent Brigham Hospital, Boston. Pp. 150; 111 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, $5.00.

THIS stands as a remarkable record of achievement on the part of one who has grown up with neurosurgery and who has directed its development in many ways. From the surgical standpoint the results recorded will be hard for succeeding generations of neurosurgeons to equal, though the author asserts that they will be even better as time goes on. One of its most striking portions has to do with the separation of the gliomas into orderly groups, each with their specific characteristics and each with their own method of reaction. This has greatly reduced the mortality in these invasive tumors. Even in the very malignant multiform spongioblastomas the mortality in the last 50 cases has been only 11.6 per cent. At the other extreme is the record of benign astrocytomas with a case mortality of 4.2 per cent and an operative mortality of 3.5 per cent.

The monograph comprises a study of the glioma, pituitary adenomas, meningiomas (to which term the author still clings), acoustic tumors, congenital tumors (craniopharyngiomas, cholesteatomas, teratomas, chordomas), metastatic and invasive tumors, granulomas, bloodvessel tumors, primary sarcomas, papillomas of the choroid plexus, and miscellaneous tumors. It is well illustrated and planned. It is a book which should be in the hands of every physician regardless of speciality, but it will be most interesting to the neurologist and neurosurgeon. The general practitioner should know it in order to realize the possibilities which neurosurgery offers.

B. A.

THE WHITE HOUSE CONFERENCE PUBLICATIONS ON CHILD HEALTH AND PROTECTION. New York: The Century Company, 1932. *Growth and Development of the Child: Part III. Nutrition.* Report of the Committee on Growth and Development, KENNETH D. BLACKFAN, M.D., Chairman. Pp. 532; various tables and charts. Price, $4.00.

"NUTRITION implies 'a study of the food substances and of the biochemical processes which utilize them.' This book, therefore, contains both an analysis of the components of diet and an account of the intricate chemistry of the body. The topics of discussion range from an appraisal of the national food supply to the feeding habits of children and the psychologic facts in nutrition."

Obstetric Education. Report of the Subcommittee on Obstetric Teaching and Education, FRED LYMAN ADAIR, M.D., Chairman. Pp. 302; various tables and charts. Price, $3.00.

"Recommendations are offered to improve obstetric practice and to lower the present high maternity death rate in the United States. Conscious that the high maternal mortality rate is a reflection on the training and education of those who are charged with furnishing maternity care, the Subcommittee made an appraisal of: The training of physicians for obstetric practice, including undergraduate training and subsequent or graduate education, the obstetric education of nurses and nursing attendants; the history, status abroad and status in this country, education and training of midwives; the obstetric education of the laity and of social workers."

THE WISDOM OF THE BODY. By WALTER B. CANNON, M.D., Sc.D., LL.D., George Higginson Professor of Physiology, Harvard Medical School. Pp. 312; 41 illustrations. New York: W. W. Norton & Co., Inc., 1932. Price, $3.50.

THE author's important experiments on the physical effects of the emotions and on the internal balancing adjustments in the body have for years been appreciated by the medical profession, as they have appeared from time to time in medical journals. This comprehensive statement, the first book that he has published since "Traumatic Shock," in 1923, not only will serve as a useful reference and summary for the profession, but should prove interesting and valuable to a wider circle of readers who are glad to get accurate information from a recognized authority on matters that have a wide human application. "The Wisdom of the Body," a title taken from Starling's Harveian Ovation, deals with the wonderful adjustments that have arisen in mammals, whereby the "extraordinarily unstable material" of which our bodies are made is coördinated by the two branches of the nervous system and a few other mechanisms into a stable unit capable

of remarkably quick, accurate and efficient adaptations. This relatively constant but dynamic condition, to which the author has given the name, *homeostasis*, is here explored and explained in terms understandable to anyone possessing the simplest familiarity with scientific terms. The epilogue, on Biological and Social Homeostasis, should especially appeal to the philosophically minded. Its inferences, if they could be widely comprehended by our publicists, would be of incalculable value in aiding the social organism to maintain a constancy of existence and in steering it safely through the reefs of our present-day difficulties and anxieties.

E. K.

NEOPLASMS OF DOMESTICATED ANIMALS. (Mayo Clinic Monograph.) By WILLIAM H. FELDMAN, D.V.M., M.S., Division of Experimental Surgery and Pathology, The Mayo Foundation. With a Foreword by CHARLES H. MAYO, M.D. Pp. 410; 193 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, $6.00.

THIS book presents extensive observations on tumors in domesticated animals together with an adequate review of the literature. Theories of etiology, including experimental studies; classification, nomenclature, incidence and general characteristics of animal neoplasms are discussed in the opening chapters. Following this are sections on mesodermal new growths, including those of blood-cell-forming tissues; melanotic and epithelial tumors; the transmissible lymphosarcoma of dogs; experimental studies, and a final chapter on preservation of tissue. This treatise should be of special value in courses on veterinary pathology, and should appeal to all students of neoplastic diseases. Of particular interest are the discussions of tumor incidence in certain species of animals and the apparent suceptibility of various breeds to certain type of tumors. H. R.

PATHOLOGY FOR NURSES. By EUGENE C. PIETTE, M.D., Pathologist and Director of the Clinical Laboratories of the West Suburban Hospital, Oak Park, Ill. Pp. 251; 65 illustrations, some in color. Philadelphia: F. A. Davis Company, 1932. Price, $1.75.

THE insurmountable difficulty of presenting etiology, pathologic anatomy, and clinical pathology in 240 small pages has been met here about as well as can be in books of this kind. It doubtless is as good an adjuvant as can be expected to the equally brief lectures assigned to this subject.

E. K.

LABORATORY TECHNIQUE. By R. B. H. GRADWOHL, M.D., Director, Gradwohl School of Laboratory Technique. Pp. 462; 148 illustrations. St. Louis: Gradwohl School of Laboratory Technique, 1932. Price, $8.00.

IN spite of the numerous works that have recently been published in this field, this book will doubtless fill a useful corner in many a laboratory. The information is accurate and presented in easily available form. Especially valuable are the newer hematologic methods (hemogram, thick drop, reticulocytes, etc.). Though only 5 pages are devoted to photomicrography and 3 to electrocardiography, these sections are treated as hints on these procedures, which make them useful adjuncts to the usual sources of information. Illustrations are collected at the back, even after the index—a procedure of doubtful value for several reasons. They are entirely original, mostly photomicrographs that really bring out the point they are supposed to illustrate, and constitute an excellent feature of the book. The space gained by the use of small type is mostly wasted by the unnecessarily large margins; the price also seems too high. E. K.

THE USE OF THE SELF. By F. MATTHIAS ALEXANDER. With an Introduction by PROF. JOHN DEWEY. Pp. 143. New York: E. P. Dutton & Co., Inc., 1932. Price, $2.00.

AFTER presenting indorsements by psychologists and the lay press, the writer, his physician having failed to relieve his throat trouble, details a new self-cure system which is in substance that mal-coördination in disease is the result of faulty "feeling" and may be cured by correct "reasoning." Patients have gone to shrines, to Coué, Mother Eddy, and presumably Sister Aimée has a list of "cures" for ready reference. Nevertheless, substantial progress will continue through regular channels. N. Y.

BOOKS RECEIVED.

NEW BOOKS.

Diseases of the Thyroid Gland. By CECIL A. JOLL, M.S., B.S.C. (LOND.), F.R.C.S. (ENG.), Senior Surgeon to the Royal Free Hospital and the Miller General Hospital; Surgeon to the Cancer Hospital, etc. Pp. 682; 283 illustrations and 24 colored plates. St. Louis: The C. V. Mosby Company, 1932. Price, $20.00.

An Introduction to Zoölogy. By ZENO PAYNE METCALF, D.Sc., Professor of Zoölogy, North Carolina State College. Pp. 425; 184 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, $3.50.

Birth, Stillbirth, and Infant Mortality Statistics for the Birth Registration Area of the United States, 1929. Fifteenth Annual Report. Pp. 373; illustrated with tables. Washington: U. S. Department of Commerce, Bureau of the Census, 1932.

Cancer: Then and Now. Publication of the New York City Cancer Committee, American Society for the Control of Cancer. Foreword by JOHN C. A. GERSTER, M.D., Chairman of Committee. Pp. 80; 35 pages of illustrations. New York: The Chemical Foundation, Inc., 1932. Price, $1.00. Can be obtained from the New York City Cancer Committee, 34 East 75th St., New York City.

"An instructive and entertaining method of bringing before the public accurate information as to what really is being done and has been done in the way of cancer control."

The Differential Diagnosis of Endocrine Disorders. By ALLAN WINTER ROWE, Director of Research, Evans Memorial, Massachusetts Memorial Hospitals, Boston. Pp. 220; illustrated with tables. Baltimore: The Williams & Wilkins Company, 1932. Price, $4.00.

Experimental Pharmacology and Toxicology. By HENRY G. BARBOUR, A.B., M.D., Yale University, New Haven. Pp. 141; 14 figures. Philadelphia: Lea & Febiger, 1932. Price, $2.75.

Excitability. A Cardiac Study. By W. BURRIDGE, D.M., M.A. (OXON.), Professor of Physiology, Lucknow University. Pp. 208; 15 illustrations. New York: Oxford University Press, 1932. Price, $3.85.

A New Physiology of Sensation. By W. BURRIDGE, D.M., M.A. (OXON.), Professor of Physiology, Lucknow University. Pp. 70. New York: Oxford University Press, 1932.

Les Réticulocytes et Les Réticulocytoses. By DR. C.-M. LAUR, Préparateur Adjoint a la Faculté de Médecine de Paris. Preface by PROFESSOR N. FIESSINGER. Pp. 160; 3 figures and 4 plates in colors. Paris: G. Doin & Cie, 1932. Price, 35 fr.

Diseases of the Spinal Cord. By WILLIAM B. CADWALADER, M.D., Professor of Clinical Neurology, University of Pennsylvania Medical School, etc. Introduction by WILLIAM G. SPILLER, M.D., Professor of Neurology, University of Pennsylvania Medical School. Pp. 204; 72 illustrations. Baltimore: The Williams & Wilkins Company, 1932. Price, $5.00.

The Child and the Tuberculosis Problem. By J. ARTHUR MYERS, PH.D., M.D., F.A.C.P., Professor of Preventive Medicine, University of Minnesota; Chief of Medical Staff, Lymanhurst School for Tuberculous Children. With an Introduction by WILLIAM P. SHEPARD, M.D., F.A.P.H.A., Welfare Director, Western Division, Metropolitan Life Insurance Company. Pp. 230; 19 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, $3.00.

Prospecting for Heaven. By EDWIN R. EMBREE, Pp. 185. New York: The Viking Press, 1932. Price, $1.75.

Diagnosis and Treatment of Diseases of the Thyroid Gland. By GEORGE CRILE and Associates. Pp. 508; 164 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, $6.50.

The Medical Clinics of North America, Vol. 16, No. 2 (Chicago Number —September, 1932). Pp. 272; 47 illustrations. Philadelphia: W. B. Saunders Company, 1932.

Acromegaly. By F. R. B. ATKINSON, M.D., C.M. (EDIN. UNIV.). With a Foreword by SIR ARTHUR KEITH. Pp. 260; 3 illustrations. London: John Bale, Sons & Danielsson, Ltd., 1932. Price, 21s.

"The monograph represents some 20 years interest in the subject of acromegaly on the part of the author. A valuable addition to the book is an interesting and instructive foreword by Sir Arthur Keith, in which his views on acromegaly find expression. The first chapter is devoted to the history of the disease from the year 1550, when a record exists of what was undoubtedly a case of acromegaly, up to the end of the year 1930." The pathologic anatomy, symptomatology, the condition of the nervous system and of the eyes, the metabolic changes, etiology, and pathogenesis receive full consideration in a most praiseworthy systematic compilation.

The Surgical Clinics of North America. Vol. 12, No. 5 (Chicago Number —October, 1932). Pp. 268; 61 illustrations. Philadelphia: W. B. Saunders Company, 1932.

Erdmann's Clinics. Excerpts Selected from the Clinics of JOHN F. ERDMANN, M.D., F.A.C.S., Professor of Surgery in Columbia University, etc. Edited by J. WILLIAM HINTON, M.D., F.A.C.S., Associate Professor of Surgery, New York Postgraduate Medical School (Columbia University), etc. Pp. 315; 39 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, $4.50.

A selection of 54 surgical topics, apparently a combination of lectures at the Postgraduate Medical School "supplemented from his Clinics and published articles."

The Colon, Rectum and Anus. By FRED W. RANKIN, B.A., M.A., M.D., F.A.C.S., Division of Surgery, The Mayo Clinic; Associate Professor of Surgery, The Mayo Foundation, J. ARNOLD BARGEN, B.S., M.D., M.S. in Medicine, F.A.C.P., Division of Medicine, The Mayo Clinic; Assistant Professor of Medicine, The Mayo Foundation, and LOUIS A. BUIE, B.A., M.D., F.A.C.S., Section on Proctology, The Mayo Clinic; Associate Professor of Proctology, The Mayo Foundation. Pp. 846; 435 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, $9.50.

NEW EDITIONS.

Anatomy of the Brain and Spinal Cord. By WILLIAM W. LOONEY, A.B., M.D., Professor of Anatomy, Baylor University College of Medicine, Dallas, Texas. Pp. 370; 153 illustrations. Second edition revised. Philadelphia: F. A. Davis Company, 1932. Price, $4.50.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

The Pathology of Bronchial Asthma.—MacDonald (*Ann. Int. Med.* 1932, **6**, 253) reviews the pathologic findings in a series of 8 autopsies on individuals who had bronchial asthma and who, in 5 instances, died apparently as an immediate result of the seizure of asthma. In discussing the pathology of the condition he notes that the chief local pathologic changes are thickening and hyaline changes of the basement membrane of the bronchi, eosinophilia, muscular hypertrophy and glandular hyperplasia depending upon the individual reaction to vagal (?) stimulation, bronchial sacculation through the mouth of the mucous glands, and epithelial changes such as hypertrophy and metaplasia. The local pathology in this report does not vary very much from the reports made in the immediate past, but of particular interest is the heretofore unnoted constitutional pathology. All of these cases conform in essential detail to the thymicolymphatic constitution, as shown by persistent thymus in every instance, hyperplasia of the lymphoid system, hypoplasia of the adrenals and of the aorta. On the basis of these constitutional findings of disturbances of this particular system the author hypothesizes a theory which he substantiates with his arguments concerning the etiology of bronchial asthma. His contention is that there exists in the asthmatic individual an inheritable hyperplastic type of constitution upon which numerous exogenous factors, ordinarily without influence on normal soil, are able to produce the allergic state, an altered reaction in the soil which is receptive. Frequently an individual may reach midlife before some apparently trivial factor initiates pathologic manifestation of this constitution, as exemplified by asthma. The author discusses rather fully the so-called bacterial asthma, a type of asthma which has been so named because it is assumed that bacteria are the specific allergens because, in turn, some type of allergen must be held, according to the views of some physicians, responsible for asthma. In the absence of any one of the

numerous protein agents which may be responsible for asthma, a bacterium or its protein is assumed to be the excitant. That such is the case seems doubtful because, irrespective of the type of asthma, bacterial or definitely allergic, the pathologic changes are all the same. He agrees with Cooke, who was unable to find any specific allergen in 48 or 50 cases of bronchial asthma, and Zinsser, who confessed to knowing only 1 instance in which the removal of the focus of infection, in this case the sinus, was responsible for relief of asthma. The summary of this paper of 25 pages, rather difficult to abstract briefly, boils down to: The local pathologic changes that occur in asthma, which have been mentioned; the disputation that there is no such thing as bacterial bronchial asthma and last, and most important, asthma and many other allergic phenomena express merely the response of a certain inheritable hypoplastic constitution of the thymicolymphatic pattern to exogenous substances.

SURGERY

UNDER THE CHARGE OF
T. TURNER THOMAS, M.D.,
PHILADELPHIA, PA.

Primary Benign Tumors of the Ureter.—MELICON and FINDLAY (*Surg., Gynec. and Obst.*, 1932, **54**, 60) report in detail a case of primary benign ureteral neoplasm, accompanied by a stricture of the ureter, ureteral and renal calculi and marked dilatation and infection of the kidney pelvis and ureter. This combination of lesions has never before been reported. From their studies the authors concluded that primary ureteral tumors are rare lesions which are infrequently diagnosed. The treatment which is safest for the patient and offers him the best chance for a cure is primary nephroureterectomy.

Irradiation of Mammary Cancer With Special Reference to Measured Tissue Dosage.—LEE, POCK, QUIMBY and STEWART (*Arch. Surg.*, 1932, **24**, 339) say that pre-operative external irradiation for mammary carcinoma is of value, as is proved by the occasional regression of tumors so treated, by the histologic changes produced and by the better clinical end-results. An efficient devitalizing dose cannot be delivered by external irradiation alone. To deliver an efficient dose one must use interstitial irradiation. The tissue dose delivered to the tumor should be measured and expressed in skin erythema units. This dose should be prescribed. Tables prepared in the physical department enable the clinician to translate into terms of skin erythema units the tissue dose delivered, whether by external or interstitial irradiation. The universal tissue dosage necessary to effect destruction of a radioresistant mammary cancer approximates 12 skin erythema doses. The safest procedure is to treat all patients with mammary cancers with the same sufficient dose, because radiosensitivity cannot always be determined before operation and the same tumor may contain radioresistant and radiosensitive areas. All pre-operative irradiation should be given within 3 weeks or less time. Six weeks should elapse following interstitial irradiations before radial amputation is performed.

Acute Suppurative Pleurisy in Children.—COHN (*Surg., Gynec. and Obst.*, 1932, **54**, 696) claims that a study of 123 cases of acute suppurative pleurisy in children and of comparative data indicate that the open method of drainage preceded by repeated aspiration is the choice method of treatment. Simple intercostal incision with open drainage is the preferred procedure in the very sick and in infants; rib resection for all other children. Local infiltration with novocain should be used whenever possible and can be used in most cases. The complications of empyema, and not the disease itself, seem to play the greater part as contributors to the mortality from this disease. Acute otitis media, in some cases complicated by acute mastoiditis, was the most frequent complication. Proper prophylactic care of the nasopharynx is recommended. Diligent after care, next to operative method, is important in surgically treating this disease. The value of operative methods must be measured not by the resulting mortality alone, but by their ability to shorten the period of convalescence, to diminish the incidence of secondary operations and to prevent chronicity.

Carcinoma of Breast.—ALDEN (*Am. J. Surg.*, 1932, **16**, 22) states that operable cancers of the breast should be subjected to the radical operation at the earliest feasible moment. The radical operation should consist in a moderate removal of skin, a wide removal of fascia and the removal of both pectoral muscles and the axillary contents. Many patients having obviously inoperable cancers are more comfortable both physically and mentally if external evidences of cancer are removed, although they die of internal metastases. All cases should receive postoperative radiation, for this method of treatment has been improving each year. Every physician seeing cancer cases should study the cases carefully; record their histories in the manner prescribed by the American College of Surgeons. It is only by concerted action and probing facts that progress can be made.

Fistulous Tracts (The Diagnostic Value of an Opaque Medium of Known Contour and Consistency).—WASSON (*Am. J. Surg.*, 1932, **16**, 57) writes that the Roentgen ray ureteral catheter is a medium of known opacity and contour. An attempt is made to draw attention to its use as a simple though valuable diagnostic aid in the study of fistulous tracts, a piece of apparatus ready at hand. Its use is indicated in the injection of those fistulas whose distribution and location are unknown and when it is therefore undesirable to use an opaque liquid or paste. It is always desirable to study the tissue surrounding the tract or cavity, and the catheter obscures this less than the usual other media. In cases presenting more than one fistulous opening, the use of more than one medium of known contour permits ready and quick recognition of each tract and aids in the differentiation of one from another.

Maggots in the Treatment of Chronic Osteomyelitis, Infected Wounds and Compound Fractures.—LIVINGSTON (*Surg., Gynec. and Obst.*, 1932, **54**, 702) believe that there can be no question as to the healing value of the maggots or larvæ treatment in all forms of chronic osteomyelitis, infected wounds and complications following fractures. The interest

aroused by the results obtained would naturally lead to an investigation of the reason for the effectiveness of this treatment. Experimental work would seem to show that it is not merely the mechanical action of the maggots, *i. e.*, feeding, rapid movement, etc., in the wound, but rather that some additional agent is developed that aids in the healing process. This conclusion seems warranted when we consider that paste made from the dead bodies is also effective as a curative agent. That additional agents are probable in effecting the cure seems to be clearly demonstrated by the use also of filtered extracts from the bodies of the dead larvæ. This would seem to point clearly to the presence of some agent which in itself is sufficiently powerful to overcome infections and permit the normal hydrogen-ion concentration balance to be established. The agent believed to effect this result is a bacteriophage. This opinion is warranted from the fact that filtered uncontaminated products derived from the bodies of larvæ in culture were quite as suitable as the living maggot, and from the fact that when these cultures were brought into contact with pyogenic organisms in petri dishes cultures were destroyed.

THERAPEUTICS

UNDER THE CHARGE OF

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A New Method of Treatment of Typhoid Carriers.—Among the measures used for the prevention of typhoid epidemics the effective treatment of typhoid carriers plays a prominent rôle. None of the methods used in the past are reliable in their effects. ONODERA, MURAKA WA and LIU (*Deutsch. Arch. f. klin. Med.*, 1931, **171**, 503), utilizing the sensitivity of the typhoid bacilli to the action of halogen compounds, and taking advantage of the fact that following the intravenous administration of tetraiodophenolphthalein, according to the technique used in cholecystography, the concentration of the substances in gall bladder is usually 5 to 8 per cent, claim that this method is useful in the treatment of typhoid carriers with infected gall bladder. *In vitro* experiments indicated that a 3 per cent solution of tetraiodophenolphthalein kills the typhoid bacilli within 24 hours, a 4 per cent solution within 12 hours, a 5 per cent solution within 10 hours and 6 per cent solution within 6 hours. Although the exposure of these solutions to Roentgen ray radiation did not alter the effectiveness of the tetraiodophenolphthalein, the authors claim that, nevertheless, the Roentgen ray exposure of the patients after the ingestion of the tetraiodophenolphthalein similarly to the technique used in cholecystography insures the effectiveness of this method of treatment. This

method is not invariably successful. Of 7 typhoid carriers 3 became permanently sterile of typhoid bacilli, 2 showed negative cultures only for 1 month and in 2 cases the method was ineffective.

The Treatment of Obesity.—Those who habitually overeat do not necessarily become overweight. There is considerable evidence that the average normal individual disposes of the excessive caloric intake by burning it up and eliminating it as heat. The principles of losing weight include decreasing the caloric intake, increasing physical activity, administration of hormones, drastic purgation and the encouragement of sweating which may yield but short-lived effects. LYON and DUNLOP (*Quart. J. Med.*, 1932, **25**, 331) studied particularly the comparative value of subcaloric diets and of thyroid extract on 35 patients of different types of obesity. The mean weight of the cases was 69 per cent above the average. All the subjects, including marked endocrine cases, lost weight while dieting. It has been found that the rate of weight-loss bears a definite relation to the caloric value of the diet: the smaller the diet the more the loss. The rate of loss is greatest at first and decreases as the diet is continued. If the total caloric intake is kept constant at 1000 the weight loss is greatest when the carbohydrate of the diet is low. It has been found that 9 grains of thyroid extract are required in order to produce a loss of weight equal to that caused by the standard 1000 calorie diet. The effect of the thyroid is proportionate to the dose given. The basal metabolic rate for the series of cases was usually within normal range on admission. The rate usually fell during the period of undernutrition, and was raised about 20 points during the administration of thyroid extract. The loss of weight when the patients were taking low diets appears to be due to the removal of fat and water from the body, but when thyroid is given the utilization of fat represents a smaller fraction of the weight loss, while the proportion of water removed from the body is greater, and some of the loss may be due to a negative protein balance.

Some Significant Observations on the Occasional Unsterility of Alcohol Solutions.—There is a general tendency to consider alcohol solutions used in surgery and medicine as necessarily sterile. Often other more reliable sterilizing agents are not used because of the belief in the absolute germicidal action of alcohol. There is some literature available in the past that that is not the case. KUHN and DOMBROWSKY (*München. med. Wchnschr.*, 1932, **79**, 791) now report an observation of great practical significance. During an investigation of the explanation of a contamination of "sterile" catgut these authors undertook to determine whether or not alcohol, benzin and ether are necessarily sterile. They arrived at the conclusion that all these disinfectant solutions may be contaminated, particularly from containers which are not sterilized. In certain solutions of 70, 80, 90 and 96 per cent solution of alcohol they were able to demonstrate aërobe and anaërobe spore-containing organisms. Of 40 examined alcohol solutions only one-half were sterile. The other half contained Bacillus subtilis, Bacillus subtilis similis, Bacillus mesentericus, etc. They could trace the source of these bacteria to the barrels from which the alcohol solution was made up. Similarly they observed that benzin and ether solutions

may be contaminated. They advise, therefore, that the containers and the water with which the alcohol is diluted should be sterilized. If alcohol is used to preserve catgut, this alcohol should be redistilled and special caution should be taken that the glass ampules are sterile. In another article KNORR (*München. med. Wchnschr.*, 1932, **79**, 793) reports his experiences on the spore content of alcohol solutions. He gives the earlier literature dating back of 1881 that points out that the commercial alcohol is not sterile. Such alcohol solutions may contain spore-bearing bacteria, but they may contain also other contaminations from the air. Thus he was able to demonstrate that a 70 per cent alcohol solution may contain Bacillus subtilis, Bacillus mesentericus, Bacillus mycoides, etc., and that these organisms grew rapidly on liver and sugar cultures. The author was able to demonstrate active spores from as small an amount as 1 cc. of alcohol solution. He advises that the alcohol solution used in surgery and medicine should be distilled under the sterile condition. The water should be also free especially of spore-bearing organisms and sterile precautions should be followed in the keeping of the alcohol solution.

NOTE.—Preparation of 70 per cent alcohol by dilution of the official 95 per cent with tap water was found by one of the editors (S. W.) to yield solutions containing living organisms. These solutions of 70 per cent alcohol did not spontaneously become completely sterile until at least 3 days had elapsed.

PEDIATRICS

UNDER THE CHARGE OF

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The Diagnosis of Early Poliomyelitis.—GORDON (*J. Am. Med. Assn.*, 1932, **99**, 1043) says that two benefits are the result of the recognition of poliomyelitis in its preparalytic stage. The public health is benefited by isolation of affected individuals at the earliest possible time. The second advantage is to the patient through early institution of treatment, whether it is carefully prescribed rest in bed, reduction of pressure by drainage of the cerebrospinal fluid or the use of supposed specific measures. Preparalytic poliomyelitis is a clinical entity distinguishable from similar conditions with a certain degree of sureness. The facts contributing to clinical recognition have been repeatedly emphasized, and yet practical experience indicates that there is a need for better general appreciation of the clinical nature of this disease. It is too often first recognized by the presence of paralysis. It is also unfortunate that in an epidemic there is a tendency to advance the diagnosis of poliomyelitis for many other and more common diseases of childhood without sufficient critical differentiation. This circumstance leads to unsatisfactory management of conditions that are not poliomyelitis, and to undue alarm about the prevalence of the specific infectious disease. The diagnosis of early poliomyelitis depends on a sound clinical suspicion substantiated by evidence derived from exami-

nation of the cerebrospinal fluid. Epidemiologic evidence aids diagnosis as cases are known to be more prevalent in August, September and October, with young children more affected than older age groups. The symptoms are those of many general infections, including typically a low grade fever, headache and vomiting. Three outstanding physical signs give the greatest aid. They are stiffness of the neck, rigidity of the spine and ataxic tremor of the extremities. The diagnosis is primarily clinical. When the evidence suggests poliomyelitis and other possibilities have been eliminated, confirmation is secured by lumbar puncture at the proper time. The cerebrospinal fluid in poliomyelitis is essentially clear, rarely of greater turbidity than slight haziness. Laboratory differentiation thus resolves itself into distinguishing infections of the central nervous system characterized by clear fluids.

The Value of Salmon Oil in the Treatment of Infantile Rickets.—ELIOT, NELSON, SOUTHER and CARY (*J. Am. Med. Assn.*, 1932, **99**, 1075) treated with salmon oil 13 children with active rickets. They recorded the response to the treatment as shown by clinical examination, roentgenograms and determinations of blood calcium and phosphorus. The oil used had been prepared from the waste products of three species of salmon, the Pink or Humpback, the Chinook or King, and the Sockeye or Red. The oil was given in doses of from 10 to 20 cc. a day, the average amount being 13.8 cc. It was well taken and well tolerated by the entire group. Response to treatment as shown by roentgenographic and blood studies was very prompt and advanced healing was brought about in from 3 to 9 weeks. Of the 6 children whose blood was studied after from 6 to 8 days of treatment, 5 showed definite increase in the serum calcium level or serum phosphorus or both. In 2 cases a normal level was reached by the end of the second week. Three children who were examined for the first time after 2 weeks from the original examination showed a return in serum calcium and phosphorus to the normal level. Only 1 child showed a greater delay in responding to the treatment. Roentgenographic evidence of response to treatment was equally prompt, 7 children showing the fresh lime salt deposits in 1 week, and 5 others in 2 weeks. One child did not show fresh deposits until the end of 3 weeks. Craniotabes improved rapidly under treatment with salmon oil. Biologic assays were made of the 3 specimens of salmon oil that were used. They showed that the Chinook and Sockeye oils were nearly equal in vitamin A potency to a composite sample made from medicinal cod-liver oils, and that Pink oil was distinctly inferior in vitamin A potency. The Sockeye and Pink oils contained twice as much vitamin D as the composite cod-liver oil, and the Chinook sample about 50 per cent more than the same sample of cod-liver oil. There is approximately 1,000,000 gallons of salmon oil available through the salmon canning industry of the Pacific states and Alaska. About three-fourths of this would come from the species of salmon used in this study and shown to be potent in the cure of rickets. About 370,000 gallons would come from the species of red salmon known to be high in vitamin A as well as in vitamin D. The production of salmon oil at low cost would be of special value at this time when the nutrition of many infants and children is suffering from lack of proper and adequate food.

Scarlet Fever.—Peacock, Werner and Colwell (*Am. J. Dis. Child.*, 1932, **44**, 494) examined 258 adults and found hemolytic streptococci in 72 (28 per cent) and 45 (17 per cent) gave positive skin reactions to the Dick test. Forty of the 45 who gave positive skin reactions received toxin for immunization. Of those retested, 87.5 were immunized to the point of negative skin reactions. On the basis of both time off duty and symptomatology, 15 per cent of the people immunized experienced severe reactions. Approximately 85 per cent of the subjects receiving injections of toxin had more or less distinct reactions. Hemolytic streptococci had disappeared from the nose and throat of 92 per cent of the subjects surveyed at the end of 28 days. Only 15 per cent of the susceptible individuals as determined by the Dick test harbored the organisms. Among the 258 subjects with positive or negative cultures, the number with tonsils and that in whom tonsillectomy had been performed were approximately equal. The erythema of the skin test averaged 19 by 18.6 mm. in diameter, and its size bore no particular relation to the grade of reaction experienced by the adults immunized. Of the adults who gave negative skin reactions, 70 per cent gave no history of scarlet fever, 24 per cent gave a history of having had the disease, and 6 per cent furnished records with no data available on that question. If the chocolate agar medium is a reliable means of differentiating nonscarlatinal from true scarlet fever streptococci, then 56.9 per cent of the organisms isolated in this series should be classified as related to scarlet fever. If the opsonification test is of differential value, 43 per cent of the organisms isolated were of scarlatinal origin, an agreement of 80 per cent with those giving no reaction on chocolate agar. Among the 186 individuals giving negative skin reactions to the Dick test, no definite case of scarlet fever developed. Of the 40 adults giving positive skin reactions, 2 contracted scarlet fever before the series of immunization was completed. Of the 5 subjects who were not immunized, 2 had severe attacks of the disease.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Stovarsol in the Treatment of Syphilis in Infants and Children.—Since very few studies in the treatment of syphilis by stovarsol have been carried on this country, the paper by Rosenbaum (*Am. J. Dis. Child.*, 1932, **44**, 25) dealing with the use of the drug in 41 children with prenatal syphilis is both interesting and timely. The dosage and system employed were those of Bratusch-Marrain, who advocated 0.005 gm. of stovarsol per kilogram of body weight for 7 days, then

0.01 gm. for 7 days, 0.015 gm. for 7 days and 0.02 gm. for 42 days, followed by a rest period of from 4 to 6 weeks. The above-mentioned courses and rest periods are repeated until the serologic tests are negative and three times thereafter. Then a rest period of 6 months is given, followed by one additional course. Stovarsol is given exclusively by mouth as an odorless white tablet readily soluble in water or milk. In 9 patients whose treatment was begun during the first year of life and continued for a year or more, serologic reversal was obtained in all cases and the clinical results were excellent. The author points out that in a similar group of 34 patients treated by the method of sulpharsphenamin and mercury, 26 per cent were Wassermann-fast at the completion of treatment. In 6 patients who were more than 1 year of age when treatment was begun and in whom it was continued for a year or more, serologic tests became negative in only 50 per cent, though clinical results were excellent. The remainder of the cases studied were under treatment for less than 1 year. Clinical improvement occurred in all patients. The serologic tests were reversed or influenced in most cases.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Cancer and Weight.—At the Huntington Memorial Hospital a study of 475 cases of epidermoid carcinoma of the cervix in which radium treatment was used has been made by LUND (*Arch. Surg.*, 1932, **24**, 145) for the purpose of determining the relationship between the prognosis of the case and the weight of the patient. He found that the percentage of cures of patients with approximately normal weight was twice that of patients who were much over or much under normal weight. A group of 79 patients with adenocarcinoma of the cervix or fundus was similarly studied, and a definite but less marked relationship was found. The obvious explanation for the unfavorable prognosis in the underweight patients is that many of them are in the terminal stages of the disease, but the reasons for poor results in fat patients are not so obvious. One factor probably is the purely mechanical difficulty of applying radium accurately in fat patients. Further than this it is purely speculative as to whether the fat person has less resistance or offers a more fertile field for malignant growth.

Diagnosis of Gonorrhea.—In an effort to determine the value of laboratory aids in the diagnosis of gonorrhea in women, JACOBY (*Am. J. Obst. and Gynec.*, 1932, **23**, 729) made a detailed study of the results

of such examinations. He believes that repeated smears should be taken and carefully examined, but the use of Gram's stain is not essential since in conjunction with a proper evaluation of the clinical examination the methylene blue stain is adequate for practical purposes. A positive smear is conclusive evidence of infection, but a negative smear, even when repeated, does not exclude the presence of a gonococcal infection. Suspicious organisms, extracellular or intracellular, should be interpreted with the clinical evidence, while pure spreads of pus cells, even without organisms present, should be regarded as suspicious evidence of gonococcal infection. Positive cultures are conclusive criteria, but are not practical or well adapted to routine practice, but a negative culture does not exclude the presence of a gonococcal infection. The complement fixation test is unreliable with the present technique since neither positive nor negative findings are conclusive and, therefore, the test in its present form should not be used. From the above opinions it is apparent that he believes that laboratory procedures are of minor importance in establishing a diagnosis of gonorrhea in women and the chief reliance should be placed upon the history and clinical evidence.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Ophthalmologic Importance of Focal Infective Prostatitis.—PELOUZE (*Arch. Ophthal.*, 1932, **7**, 372) believes that no study of focal infection in the male is complete without investigation of the prostate. After the age of 30 years prostatitis is usually an infection secondary to a distant focus, predominantly in the teeth or tonsils. Occasionally it is caused by gall bladder disease, by influenza or by some other systemic infectious disease. In a series of 100 unselected cases of focal infective prostatitis with distant absorptive symptoms, only 7 patients had ever had gonorrhea, 69 had infected tonsils, 61 had infected teeth and 46 both. Of all men with symptoms of a focal infection 72 per cent have prostatitis and at least 35 per cent of all men above the age of 35 years have prostatic infection. Infections of the nasal accessory sinuses are not important primary foci for prostatic infections. Focal infective prostatitis usually gives no subjective symptoms and its diagnosis rests solely on the microscopic study of the digitally expressed prostatic secretion. It does not recover spontaneously and it cannot be cured by local treatment until the causative foci have been removed. In the treatment of prostatic infection associated with ocular lesions the prostate should not be massaged oftener than twice a week and not

within 3 days of the subsidence of a focal reaction caused by a previous treatment. Treatment should be continued for at least 3 months. While true gonorrheal iritis is very rare, a large percentage of focal infective ocular lesions, such as ulcerative keratitis, iritis, uveitis and choroiditis are caused primarily, or more often kept up secondarily, by prostatic infection. The relationship can be demonstrated by the occurrence of a focal reaction in the affected eye following manipulation of the prostate. If such a reaction does not occur following one of the first few treatments the prostate can be practically acquitted as a focus. In subsequent treatments the massage should be so graduated as to prevent the occurrence of any or at least of too severe a reaction. If the eye condition becomes worse in spite of careful massage, the treatment should be temporarily discontinued. If the eye condition improves at first and later remains stationary search should be made for recurrent foci elsewhere, in the teeth, tonsils or nasal accessory sinuses. Massage of the prostate should not be continued while any vaccine is being administered to the patient.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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Glossitis in Pernicious Anemia.—In reporting 2 personally encountered cases, MAGER (*Monatschr. f. Ohrenh.*, 1932, **66**, 315) emphasizes the importance of glossitis as an early clinical manifestation of pernicious anemia; and of making thorough hemocytologic examinations in all instances of glossitis and stomatitis. Subjectively, intermittent lingual and buccal pain, burning and soreness—intensified by ingestion of hot and highly acid foods—were the chief symptoms. Objective findings consisted of a thickened tongue with a smooth, inflamed-looking surface and edges. At times lingual, palatine and buccal vesicles occur.

A New Test for the Diagnosis of Disease of the Inner Ear.—Movement of the ears on acoustic stimulation may be voluntary or involuntary. As a voluntary act, it is usually associated with intent listening and often has been designated as "pricking up the ears." Involuntary auricular movement occurs in animals and man. In the experimental animal it is called Preyer's reflex, which is commonly accepted as physiologic proof of auditory integrity. This reflex movement has also been discerned in persons presenting pathologic conditions of the auditory apparatus. This involuntary phenomenon in human beings has been termed the "auricle reflex" by FABRICANT and SOMMER (*Arch. Otolaryngol.*, 1932, **16**, 360). Inasmuch as, apparently, no practical clinical utilization of this reflex in man has been made, these authors produce evidence to show that the "auricle reflex" is not rare and of some diagnostic significance. The "auricle reflex" is a rhythmic jerking of the auricular appendage. Usually the movements are confined

to a portion of the auricle; if the excursions involve the entire ear, they are of small amplitude—as a rule. The reflex best can be elicited by holding the middle C 1 tuning fork to the concha, or by placing over the forehead or mastoid prominence. A positive "auricle reflex" was encountered in 55 of 198 cases. In only one of the 55 was the ear apparently normal. The reflex occurred more frequently in patients with lesions of the inner ear than in those with combined involvement of the middle and inner auditory apparatus. No movement was noticed in persons with unilateral cochlear lesions, otosclerosis or complete deafness. Having observed that the "auricle reflex" most frequently associated with progressive deafness, the authors explain its mechanism on the basis of increased tonus of the auricular musculature. They conclude that the presence of the reflex should suggest a primary involvement of the cochlear nerve.

RADIOLOGY

UNDER THE CHARGE OF
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Radiotherapy of Pituitary Tumors. — Thirteen cases of pituitary tumor were subjected to Roentgen ray therapy and observed at trimonthly intervals by HARRIS and SELINSKY (*Radiology*, 1932, **18**, 777). Seven of the 13 patients were distinctly benefited by the treatment and 1 showed temporary improvement. Amelioration of headache and improvement in vision were most frequently noted. In no case did the symptoms completely disappear. Failure to respond to treatment is highly suggestive of a cystic tumor (craniopharyngeal pouch cyst).

Recent Advances in Heliotherapy as Applied in Pulmonary Diseases.—It is a generally accepted tradition, says FORSTER (*Arch. Phys. Ther., X-Ray, Radium*, 1932, **13**, 214), that while heliotherapy is efficacious in extrapulmonary tuberculosis its use is contraindicated in the pulmonary form of the disease. He feels that the explanation of this fundamental mistake lies in overdosage, and that it is most essential to study and supervise most carefully the reaction of the individual patient. He has noted many times that certain patients were unable to take more than a few minutes of sun. If a patient with tuberculosis of the wrist receives an overdose of sun he will undoubtedly sustain a reaction which may be unfavorable, but the damage is not irreparable. When pulmonary tuberculosis is being treated by heliotherapy and an unfavorable reaction is produced the harmful effect may continue indefinitely. The author chooses for treatment those patients with pulmonary disease who have already shown power to resist their toxemia. Patients with acute advancing pulmonary tuberculosis can only expect harm from sun treatment, but as soon as the

disease has shown evidence of developing chronicity, which is the beginning of cure, then carefully supervised heliotherapy almost invariably has a favorable effect on metabolism and is an aid to the patient in acquiring resistance to the disease. When patients show marked sensitivity to sun treatment lamps may be used until tolerance is built up to the point where the sun can be borne. In spite of the efforts of lamp manufacturers to reproduce all the elements of the spectrum, it is becoming recognized that natural heliotherapy has advantages over any other form of light treatment.

Pulmonary Asbestosis. — The fact that the inhalation of asbestos dust produces an effect on the lungs was observed many years ago, but the serious results which follow have only recently been recognized. SPARKS (*Radiology*, 1931, **17**, 1249) considers the roentgenologic appearances quite typical in advanced cases. The movement of the diaphragm is limited and its outline tends to be indistinct or uneven. There is clouding in the costophrenic angle due to pleural thickening which latter often extends along the costal margin to the apices. The lung fields at first show slight increase of density in the lower zones without accentuation of the bronchial markings. Sometimes small calcareous deposits are scattered through the lower zones, but they are less dense and more irregular in outline than calcifying tubercles. Later, dense patches and a fine network of fibrosis appear in the lower zones and may extend into the mid zones.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF
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On the Problem of Delinquency.—LEVY (*Am. J. Orthopsychiat.*, 1932, **3**, 197) lists three major groups of influence responsible for delinquency: (1) Social forces; (2) personality traits, and (3) mental conflict. Rarely does one group predominate; usually it is a mixture of two or all three groups, with the balance in favor of one or the other group. He cites examples to illustrate the part played by the different causal factors and concludes with the statement that when these factors are determined and grouped, treatment can be easily instituted in logical relation to them.

Creation and Handling of Resistance in Clinical Practice.—ALLEN (*Am. J. Orthopsychiat.*, 1932, **3**, 268) defines resistance as the effort made by individuals to handle negative feelings manifested mainly by antagonism, distrust, dislike, and so forth, and it is held by the author that full participating coöperation cannot be had until these resistive manifestations are allowed free expression. We should see an individual as one with a problem of his own and act as clarifiers, not cor-

rectors, which happens when we project our own ideals into the treatment program and insist that the patient be moulded according to our own point of view. Oversympathy with the patient may create resistance in the parents which will be directed against the clinic. We can avoid creation of resistance by seeing the problem objectively by allowing full and free expression of negative feelings. No clinic member should show force, coercion, blame, shame or any feeling that would suggest anything but an unbiased observer with a desire to help.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
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The Occurrence of Intranuclear Inclusions in Monkeys Unaccompanied by Specific Signs of Disease.—COVELL (*Am. J. Path.*, 1932, **8**, 151) found intranuclear inclusions in 20 out of 60 monkeys. The animals were dead of various diseases. The inclusions were located in nasal mucosa (6 cases), tracheobronchial mucosa (5 cases), alveoli of the lungs (12 cases) and intrahepatic bile ducts (3 cases). The inclusion nuclei were characterized by margination of all basophilic chromatin on the inner surface of the nuclear membrane, clumping of the acidophilic material in the center of the nucleus and the appearance of a clear halo between the inclusion and the nuclear membrane. The author assumes that these inclusions represent the presence of an unknown virus infection of low virulence and points out the importance of being aware of the spontaneous occurrence of such inclusions in an animal like the monkey which is used so much in the study of filtrable viruses. This report comes as a sequel to that of STEWART and RHOADS (*Proc. Soc. Exper. Biol. and Med.*, 1929, **26**, 664) who were first to describe spontaneous inclusions in monkeys.

Polypi Coli.—Polypi of the colon are found in two conditions: The first, polyposis coli universalis, occurs in the young adult or adolescent and manifests itself in a large number of adenomatous polypi thickly scattered over the whole length of the colon. Polypi coli, on the other hand, are seen most commonly in later adult life, and are found in small numbers. Histologically the lesions in the two conditions are similar. In 1100 consecutive autopsies studied by SUSMAN (*J. Path. and Bact.*, 1932, **35**, 29), 65 cases of polypi coli (with a total of 198 polypi) and 1 of polyposis coli universalis were encountered. The polypi did not have any particular site of election in the colon. The well-known relation to carcinoma was substantiated—of the 66 cases 15 had carcinoma of the large bowel. Viewed from the opposite standpoint, 34 cases of cancer of the colon came to autopsy during the period covered by this investigation. In 15 of these, polypi were also present and in 5 of the

15, actual malignant polypi were found. The sex distribution showed a distinctly higher incidence in males (77 per cent). Of the patients with polypi coli 93 per cent were over 40 years of age.

The Dynamic Bronchial Tree.—MACKLIN (*Am. Rev. Tuberc.*, 1932, **25**, 393) studied the movement of the lung by means of the Roentgen ray and anatomic dissection. He found that the lung root constituted a pedicle from the bifurcation of the trachea to the roentgenologic hilum. It is normally flexible, permitting the air and blood channels to stretch and widen in inspiration and to shorten and narrow in expiration, but this flexibility may be impaired by pathologic processes, and then the function of the lung is handicapped, particularly in the region lying above and behind the hilum, that is, in the district which is preferred by the tuberculous process. The connection of root movement restriction with the precipitation of tuberculous lesions is suggested. Diagrams are employed to clarify the ideas presented. Need for further Roentgen ray research to ascertain the normal range of root movement under all conditions is emphasized.

Bacteriological Investigations on the Blood, Synovial Fluid and Subcutaneous Nodules in Rheumatoid (Chronic Infectious) Arthritis.—A careful bacteriologic investigation of the blood, synovial fluid and subcutaneous nodules in patients suffering from rheumatoid arthritis has been recently completed by DAWSON, OLMSTEAD and BOOTS (*Arch. Int. Med.*, 1932, **49**, 173). Using the elaborate technique of Cecil, Nicholls and Stainsby, 105 blood cultures were made on 80 patients. Blood from healthy individuals and sterile agar were used as controls. The organisms obtained by this method, the majority of which were coarse Gram-positive bacilli, diphtheroid forms and staphylococci, could not be regarded as of any etiologic significance, and were also frequently present in the control material. Aërobic and anaërobic cultures of 23 specimens of synovial fluid and 12 subcutaneous nodules yielded similarly negative results.

The Relation of the Liver to the Disposal of Hemoglobin.—The deposition of iron pigment in the liver, kidney and spleen was studied by MUIR and YOUNG (*J. Path. and Bact.*, 1932, **35**, 113) by injecting solutions of hemoglobin into rabbits. After a single injection of a considerable amount there was no evidence of the hemoglobin being taken up by the liver cells or Kupffer cells. Nor was there any present in the bile. On the other hand, the cells of the convoluted tubules of the kidney gave a diffuse reaction for iron on histologic examination. The spleen did not show any significant change. The next step was the study of "chronic hemoglobinemia" caused by daily intraperitoneal injections of the hemoglobin solution. In these experiments the liver did show a slight increase in iron, which was accumulated mostly around the central veins, but the amount was not nearly so great as in the anemia produced by a hemolytic serum. The kidney contained a great deal of hemosiderin, nearly all of which was in the proximal convoluted tubules. The spleen also contained an increased amount of hemosiderin over the normal. The authors conclude that these experiments do not support the view that hemoglobin as such is taken up by the cells of the liver and broken up by them.

Psittacosis: Report of 5 Cases.—An outbreak of psittacosis, 5 cases in one family, traced directly to a group of parrakeets imported from Cuba by a returning tourist, was studied by RABINOWITZ and LIVINGSTON (*Arch. Int. Med.*, 1932, **49**, 464). Two of the patients died. Analysis of the histories of the 5 cases brought out the following important features. The incubation period was about 9 days. The disease was insidious in its onset, beginning with chilly sensations, malaise and fever. The patients soon became decidedly toxic, but pulmonary signs did not appear until the disease was well advanced. Roentgen ray showed dense well-defined consolidation of part of a lobe; crepitant râles in the involved area. Slight cough was usually present, accompanied by scanty, extremely thick, mucoid expectoration, occasionally blood-tinged. The leukocyte count ranged between 9000 and 13,000, with relative increase of polymorphonuclear cells. An outstanding feature was the tendency to venous thrombosis. In the one postmortem examination the important findings were lobular pneumonia, thrombosis of the pulmonary artery, pulmonary veins, iliac vein and splenic vein, gastroenteritis and multiple hemorrhages of the spinal cord with chromatolysis, satellitosis and fat replacement of the anterior horn cells. The psittacosis virus was demonstrated in the liver, lungs and spleen. It was also found in the sputum of one of the patients and in the liver and spleen of one of the parrots. Incidentally, this bird was apparently healthy.

A Case of Reticulum Cell Carcinoma of Thymus.—McDONALD (*J. Path. and Bact.*, 1932, **35**, 1) studied a tumor, which formed a pedunculated, cystic mass, measuring 6 by 4 cm. in area, and was located immediately below the great vessels as they leave the heart, in a male, aged 59 years. The tumor had a well-defined fibrous capsule, and the parenchyma was diffluent and grayish-red, suggesting a necrotic condition. Microscopically the two main types of cells were seen. The first was a large round, oval or polyhedral "epithelioid" cell very similar to the reticulum cell of the thymus. Scattered among these cells were others morphologically identical with small lymphocytes. The "epithelioid" cells grew in strands in close relation to the vessels; in some places they were arranged in flattened plaques almost like squamous epithelium. There was no tendency toward an alveolar or perivascular arrangement of the parenchyma. On the whole, there was a slight superficial resemblance to the medulla of the thymus, although Hassall corpuscles were absent. There were also some inflammatory changes. The tumor was only locally malignant, there being no distant metastases or infiltration of the neighboring lymph nodes. There were some deposits in the adipose tissue at the tumor base, but these were considered to be portions of involuted thymus. A single Hassall corpuscle was found in one of these deposits.

Sacculated Intracerebral Aneurysm of the Middle Cerebral Artery.—A case is reported by CHASE (*J. Path. and Bact.*, 1932, **35**, 19) of a single, sacculated aneurysm arising in the middle cerebral artery and situated entirely within the brain substance. The patient was a woman, aged 30 years, 8 months pregnant. The only complaint had been a persistent, dull, generalized headache for the preceding 6 months. She was

admitted in coma, and died on the operating table after a Cesarean section had been performed and a healthy, live baby delivered. At autopsy the ruptured aneurysm, measuring 3.2 cm. at its greatest diameter, was found. There was also an anomalous distribution of the vessels at the base of the brain—absence of both posterior communicating arteries and anomalous position and branching of both anterior choroidal arteries. The author discusses the three possible etiologic factors: (1) inflammation, (2) degenerative changes and (3) congenital structural malformations. He decided that the latter was the important factor in this case. This decision is reached by exclusion of the first two and the presence of developmental vascular malformations. In addition to those mentioned above, definite defects in the media of two vessels at the acute angle of branching were found; it is assumed that the aneurysm arose in a similar weak point at the division of the right middle cerebral artery into its three large cortical branches.

Histochemical Studies by Microincineration of Normal and Neoplastic Tissues.—Comparative histochemical studies of normal and neoplastic tissues by an improved method of microincineration were undertaken by SCOTT and HORNING (*Am. J. Path.*, 1932, **8**, 329) with the confirmation and extension of the earlier observations of Policard and Doubrow in this field. Several types of human breast carcinomas along with three varieties of transplantable mice tumors and normal control tissue were subjected to incineration in an electric quartz oven at 650° C. and the inorganic residue studied in dark field illumination. Apart from cancerous tissue remaining carbonized longer than normal tissue, it was observed that the distribution of the mineral ash deposits was more abundant and concentrated in the tumor than in the surrounding stroma. Both nuclei and cytoplasm of the tumor cells moreover contained more ash than normal cells, the deposits being concentrated toward the periphery of the nuclei, which also contained more iron oxid than seen in the controls. The difference in ash content between the neoplastic tissue and the stroma was also observed in the rodent tumors but was not so striking as in the human material. The authors felt that their results demonstrate the functional differences between cancerous growths and normal tissues, and that a close similarity exists between the distribution of the mineral salts in embryonic and malignant cells.

Subcutaneous Nodules in Chronic Arthritis.—An histologic and bacteriologic investigation of the subcutaneous nodules occurring in chronic arthritis has been carried out by CLAWSON and WETHERBY (*Am. J. Path.*, 1923, **8**, 283). These structures, which varied in size from 5 mm. or less to 3 cm., were present in 29.5 per cent of 200 cases. They were found most frequently in the upper extremities, were often multiple and sometimes occurred bilaterally in the same location. In the gross, areas of necrosis surrounded by fibrous tissue were usually seen. Microscopically these necrotic areas contained many polymorphonuclear leukocytes and were surrounded by mononuclear and multinuclear cells, often showing a palisade arrangement similar to that seen in the heart valves in rheumatic endocarditis. Small abscesses containing streptococci were also frequently noted. A perivascular inflammatory

response accompanied by endothelial swelling was present. The nodules were surrounded by varying amounts of fibrous tissue. The strong similarity noted between these structures, the subcutaneous nodules of rheumatic fever and those experimentally produced by streptococci of low virulence suggest to the authors a common etiologic agent. Macerated nodules, cultured in beef infusion broth, yielded Gram-positive green-producing streptococci in 12 out of 17 cases (70.6 per cent).

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Immunization with Bacterial Bodies Against Tetanus.—In a further study, COLEMAN with GUNNISON (*Am. J. Hyg.*, 1931, **14**, 526) states that during the World War Tulloch showed by the agglutination reaction that Cl. tetani could be differentiated into 4 serologic types which have since been extended to 9 by other workers. Tulloch investigated several phases of the question of type specificity and attempted to correlate his results with his clinical observations, his idea being that perhaps serums of greater prophylactic value could be produced if bacterial bodies as well as filtered toxin were used in the immunization of animals. These experiments were "suggestive" but very inconclusive. It has been reported by workers in China that antispore and antibacterial serums "practically free from antitoxin" which have type specific protective value against infection with Cl. tetani may be produced in rabbits. Confirmation of this conclusion has not been possible. The present authors were not able to produce by any method serum with bacteria or spores in rabbits, goats or guinea pigs which contained antibacterial or antispore substances or antibodies effective in preventing tetanus infection in guinea pigs. None of these serums enhanced the protective value of purely antitoxic serums. Antitoxic serums produced with the organisms of Cl. tetani as well as with toxoid are no more effective in preventing or delaying infection than those produced with filtered toxoid or toxin alone, the unitage in each case being approximately the same.

Mosquitoes Transported by Airplanes.—STAINING METHOD USED IN DETERMINING THEIR IMPORTATION.—GRIFFITTS and GRIFFITTS (*Pub. Health Rep.*, 1931, **46**, 2775), by means of observations under experiment and under natural conditions, arrive at the following conclusions: That certain types of airplanes carry mosquitoes (particularly Aëdes ægypti and Culex quinquefasciatus) has been proved. With conditions at airports such as would permit of many mosquitoes getting

aboard, it might be expected that approximately one-fifth of the original number would be transported for a long distance—at least 1250 miles—in 1 day, with repeated landing and the opening of doors, hatches and windows and refueling, unloading and loading taking place. Under average natural mosquito production conditions about airports, heavy infestation of aircraft (like the "loading" of planes in these experiments) would not be expected and, consequently, mosquitoes in only small numbers would make the trip. However, even one infected, or infective, Aëdes ægypti might be the means of starting an epidemic. Notwithstanding the fact that airplanes may, or do, transport mosquitoes, this mode of introduction of mosquito-borne disease is probably secondary in importance to the importation of infected man. With the relatively small number of mosquitoes carried by aircraft and the facility with which airplanes may be freed from mosquitoes at ports of departure, it may safely be concluded that, while there is a recognized potential danger, there is no obstacle to the efficient treatment of airplanes so as to destroy mosquitoes and avoid retardation of air traffic progress.

Case Fatality of Communicable Disease.—WOOD (*J. Prev. Med.*, 1932, **6**, 87) states that case-fatality ratios are the proportion of deaths which actually occur in a known number of cases of any disease, that is, the number of cases per death. Case-fatality ratios indicate the completeness of reporting of a disease and show the virulence of the disease. Correct case-fatality ratios depend upon complete reporting and the determined actual number of deaths among the persons whose cases have been reported. Correct ratios cannot be computed from the usual vital statistics tabulations. The following case-fatality ratios are approximately correct: diphtheria, 15 to 19 cases to 1 death; measles, 500 to 1; scarlet fever, 100 to 1; typhoid fever, 8 to 12 cases to 1 death; whooping cough, 125 to 150 cases to 1 death. Any state whose ratio of reported cases to recorded deaths falls much below those figures is obtaining very incomplete reporting, and therefore incomplete control over its quarantinable diseases.

Vaccine in the Prevention of the Common Cold. An Experiment.—BROWN (*Am. J. Hyg.*, 1932, **15**, 36) claims that the statistical results of the experiment show little, if any, improvement as regards common colds in the experimental group as a whole compared with the control group. Individuals in the experimental group appear to have received some benefit. This is in accord with the findings that the group as a whole was not completely desensitized to the particular antigens used. Better results may be possible with an increased dosage of the vaccine or by employing with each individual the particular antigens to which he may be shown sensitive.

Syphilis.—PARRAN (*Am. J. Pub. Health*, 1932, **22**, 141) considers syphilis from the point of view of the epidemiologist. He states that epidemiologic evidence argues for the practicability of control and eradication through direct public health action. Syphilis appears to spread chiefly through a series of localized outbreaks which can be traced to comparatively few determinable sources; the bulk of infection in the white race is concentrated in the cities; most of the cases have a

limited period of infectivity, and elimination of infectious sources will have a cumulative effect on the trend. The existence of an unknown percentage of subclinical cases, many of which are infectious, does not, in the opinion of the author, invalidate the major conclusion. A large proportion of cases are acquired from untreated and inadequately treated cases. These can be recognized by clinical examination and serologic tests and can be made noninfectious by treatment. By these available methods it seems practicable to eradicate syphilis as a public health problem. CRABTREE and BISHOP (*Ibid.*, p. 157) have made a Wassermann survey of a group of negro families in Tipton County, Tenn. Of a total of 2323 individuals of all ages tested, 602, or 26 per cent, were found to have positive Wassermanns; 86.6 per cent of these were between the ages of 15 and 50 years. Of 562 cases placed under treatment and observation, 62 were classed as congenital and 464 as acquired syphilis. When persons are infected with syphilis the likelihood that it will not be apparent to females is 1.8 times that of it not being known to males. Of 195 cases giving a history of known primary lesion, 18.5 per cent cent stated that the lesion was acquired within the past year. Data collected allowed for the estimation that the annual morbidity rate for cases of acquired syphilis in Tipton County, Tenn., is approximately 4233 per 100,000 population. Treatment of cases is shown to be wholly inadequate. The likelihood of a pregnancy resulting in either a stillbirth or miscarriage when either parent has a positive Wassermann is 8.2 times that of such an occurrence when neither parent has a positive Wassermann.

Study in the Epidemiology of Diphtheria in Relation to the Active Immunization of Certain Age Groups.—GODFREY (*Am. J. Pub. Health*, 1932, **22**, 237) states that the injection of 50 to 70 per cent of children over 5 years of age with 3 doses of toxin-antitoxin has failed in numerous instances to produce any marked effect on the diphtheria incidence of a community. The immunization of 30 per cent or more of children of the under 5-year age group in addition to more than 50 per cent of children 5 to 9 years has in several instances produced an immediate and striking decline in the diphtheria rate of the community as a whole. The promptness of this seeming response suggests that a high degree of immunity is quickly acquired by a majority of those given 3 doses of toxin-antitoxin. It is a matter probably of a few weeks rather than several months. The point is worthy of further investigation. In only 2 instances known to the writer has a community that had attained 30 per cent immunization of its under 5-year age group suffered even a moderate epidemic. It is possible that immunization of the under 5-year age group should not be uniformly distributed through the community, but should be largely concentrated in sections of highest prevalence if diphtheria is prevalent; if not, then in the congested areas. The present study is given as a working hypothesis, worthy of trial as a means of quickly ridding a community of epidemic diphtheria. Much more data from more varied sources are necessary to establish its validity. To this end uniformity in the tabulation of immunization statistics is a necessity. The Committee on Administrative Practice and all health departments should adopt the standard age grouping in their tables, should classify immunizations by single years of age up to

10 years and should annually or oftener so tabulate their material as to show the present status. It is suggested that the unrecognized case rather than the healthy carrier is responsible for the occult infections occurring epidemics or periods of high prevalence. It seems not improbable that many mild nasal cases would be discovered if diligently sought. Such cases are the ones most likely to spread infection. Finally it should be clearly understood that this presentment is in no sense a plea for any community to stop work when it has attained a 30 per cent immunity. That figure may be much too low. Active immunization, like antitoxin, was introduced on a wholesale scale during a period when diphtheria was receding from a period of high epidemicity. It is, therefore, the more difficult to measure its effect. The immunity conferred may not suffice for an organism of greater invasiveness, virulence and pathogenicity. In any event, the only reasonably sure protection for the individual is individual immunization. The one unvaccinated individual in the city may be the gas station man who serves an itinerant smallpox case. The one infected mosquito may bite a susceptible.

A Further Study of Brucella Infection in Iowa.—HARDY and his associates (*U. S. Pub. Health Rep.*, 1932, 47, 187) report a total of 156 cases of undulant fever in Iowa on the basis of the agglutination reaction. The graver forms of the disease are rare, and the disease is not regarded as an important health hazard. Cases generally were sporadic though 3 cases were traced to one herd and 2 to another. Farmers and farmers' wives contributed about one-half of the cases with the remainder scattered in different groups of the population. As is usually true, males greatly outnumbered females among those infected. There was no case below the age of 10 years. Hogs and cattle are of about equal importance as sources of infection. The patients infected from hogs suffer a more severe form of infection than hose infected from cattle. In 3 cases Brucella melitensis, variety *abortus*, were isolated from the human case and from the animal suspected of being the source of the disease.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 17, 1932.

The Oxidation of Cystin in a Nonaqueous System.—GERRIT TOENNIES and THEODORE F. LAVINE (Lankenau Research Institute, Philadelphia). Of the 7 theoretically possible compounds, 2 acids and 5 anhydrids, that are, according to the state of oxidation of sulphur, intermediate between cystin and cysteic acid, none has been isolated as yet. The authors attempted to devise a method by which some of these compounds could be prepared. Since oxidation in aqueous medium seems

to involve splitting of the -S-S- linkage and formation of cysteic acid as a consequence, it was attempted to dissolve and oxidize cystin in a nonaqueous and nonalcoholic medium, in order to avert splitting of the sulphur linkage. Intending to avoid the necessity of obtaining the desired solubility in a nonaqueous medium by a change of the molecule by substitution, the authors studied the formation and solubility of salts of cystin in the absence of water. It was found that cystin dissolves easily in a methylalcoholic 1 N HCl solution and that the specific rotation in such a solution is little different from that of an aqueous HCl solution of the same concentration. In the alcoholic solution, however, esterfication takes place on standing. A satisfactory system was found in an anhydrous solution of perchloric acid in acetonitrile. A solution of 70 per cent aqueous perchloric acid in acetonitrile is made anyhydrous by addition of an amount of acetic anhydrid equivalent to the water present. In this medium perchloric acid dissolves an equivalent amount of cystin and the $\frac{N}{10}$ solution appears stable for at least 4 weeks. Cystin, when oxidized in such a solution by benzoylhydroperoxid at low temperatures, takes up a maximum of 4 oxygen and a precipitate is obtained which is not uniform in composition but approaches the formula 2 $R\text{-}SO_2\text{-}SO_2\text{-}R + 1\ HClO_4$. This product is extremely hygroscopic and the acidity of its aqueous solution increases rapidly with time, approaching 1 acid for each sulphur. The aqueous solution is capable of reducing iodin as well as of oxidizing potassium iodid. While the nitroprussid test for -SH groups is not produced by the compound in presence of cyanid, a strong test is given if subsequent to the action of iodid, which is oxidized to iodin, cyanid is applied.

A Study of the Nonfermentable Fraction of "Blood Sugar."—F. M. KERN and L. S. SMELO (Department of Physiological Chemistry, University of Pennsylvania). It has been known for some years that the total reducing power of blood, as measured by the reduction of alkaline copper solutions, represents other substances besides "true" sugar. The nonsugar reducing substances ("saccharoid") may be distinguished from the sugar, since they are not fermentable by yeast. Under certain conditions (such as high blood sugar) the indirect technique of Somogyi for the determination of the "saccharoid" was unreliable. Excellent results were obtained when the "residual reduction" was determined directly, using the Shaffer-Hartmann reagent (modified by Somogyi) and filtrates obtained by the Folin-Wu technique from blood which had stood in contact with a washed, active yeast suspension.

The quantity of "saccharoid" in dogs' blood was found to be 27 mg. (±6 mg.) per 100 cc., while in cats' blood it had an average value of 32 mg. These figures are practically identical with that usually accepted for human blood. This value has been found to be practically independent of variations in diet, which have included meat exclusively (for 28 days), high protein (for 50 days), low protein-high carbohydrate (for 21 days), and a mixed hospital regimen (30 days).

It was not possible to demonstrate a diurnal variation in the saccharoid content of blood. The administration of insulin and adrenalin produced the usual changes in total reducing substances, but the

"saccharoid" remained unchanged in quantity. Fasting (for 72 to 96 hours) is the only experimental condition thus far encountered which appears to have caused a change (slight diminution) in the value of the "saccharoid."

Acute Experimental Glomerulitis.—NEIL MCLEOD and GEORGE G. FINNEY (Medical Clinic, School of Medicine, Johns Hopkins University, Baltimore). Focal, scattered glomerular lesions and more diffuse changes involving glomeruli, tubules and interstitial tissue were produced by injection of heated suspensions of green streptococci into the left renal artery of rabbits. The uninjected right kidney served as a control and proved to be normal in every case. Lesions were produced in 16 per cent of 24 normal rabbits and in 45 per cent of 33 animals which had been rendered skin-hypersensitive by repeated intracutaneous injections of green streptococci. In the "sensitized" group the development of glomerulitis bore no relation to the degree of skin sensitivity, to the presence of a secondary skin reaction, or to a specific eye reaction. Of four strains of green streptococcus used, two produced renal lesions more readily than did the others. Glomerular changes included epithelial and endothelial cell proliferation, crescent formation, cellular exudate, fibrin deposits. It is suggested that this glomerulitis is not a reflection of an allergic state.

Tumors in Frogs.—B. LUCKÉ (Laboratory of Pathology, University of Pennsylvania). This preliminary report is based upon a study of 18 frogs (R. pipiens) with renal tumors. The tumors were generally located in both kidneys, and appeared as whitish nodules. Histologically they corresponded with adenocarcinomas. The nature of this neoplastic disease is being investigated.

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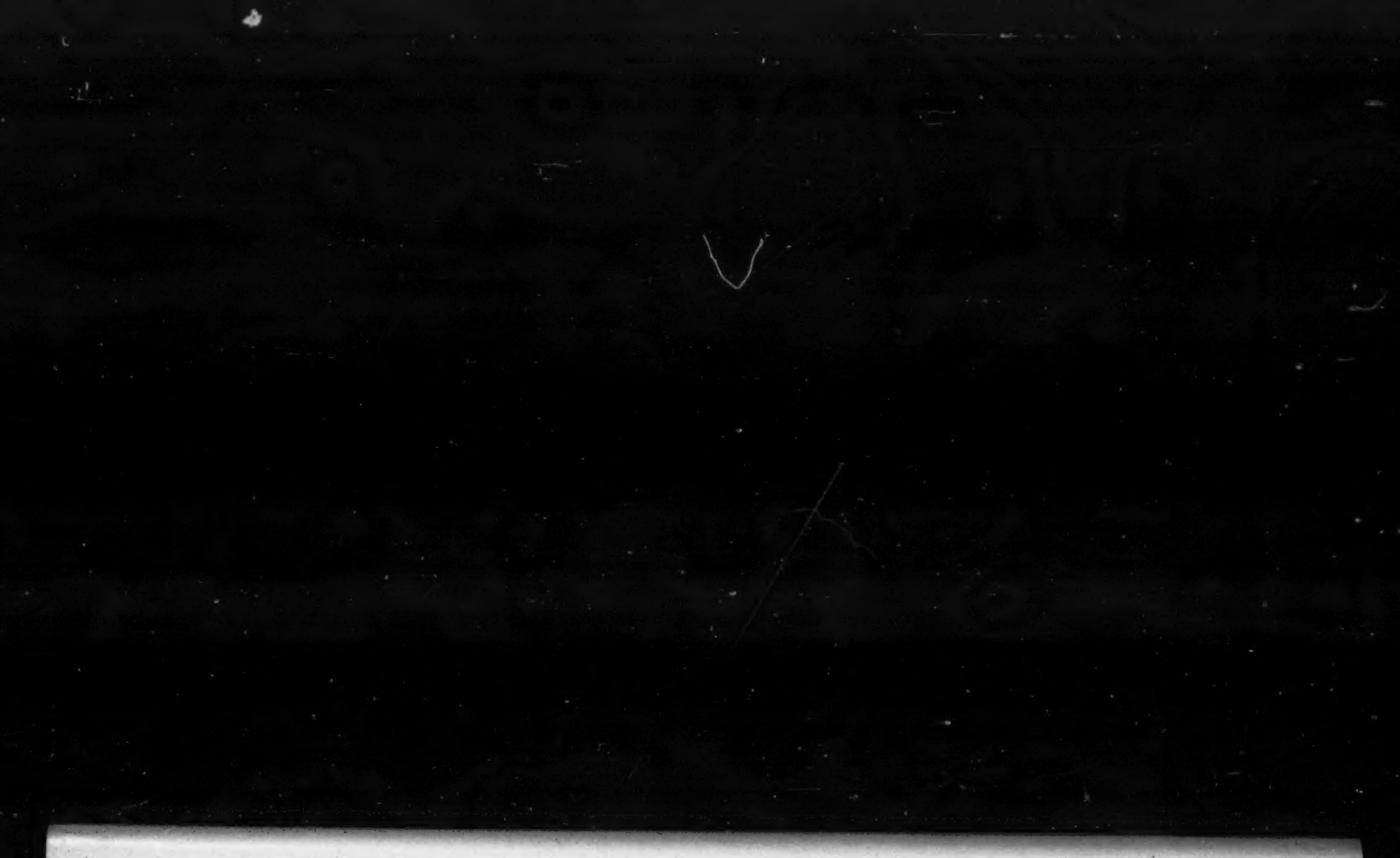

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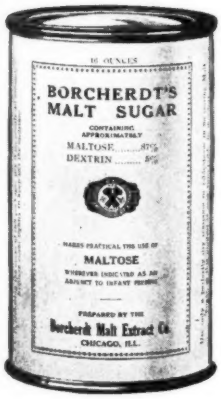

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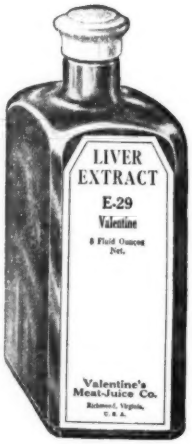

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